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     (FILE 'HOME' ENTERED AT 08:06:01 ON 11 APR 2001)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 08:06:32 ON 11 APR 2001
               E WO98-CA992/AP,RPN
L1             1 S E3
               E GEORGES E/AU
L2            57 S E3,E5,E6
               E WANG Y/AU
L3          3678 S E3-E40
               E WANG YING/AU
L4          1675 S WANG YING?/AU
L5          5407 S L2-L4
L6             3 S L5 AND ANNEXIN
               E ANNEXIN/CW
L7          1662 S E3,E4
               E ANNEXIN/CT
L8          1662 S E3-E23
               E E13+ALL
L9          2164 S E21,E20+NT
L10            2 S L5 AND L7-L9
L11            3 S L6,L10,L1
L12            3 S L5 AND (P40 OR P 40)
L13            1 S L12 AND L11
L14            5 S L11-L13
               E MULTIDRUG/CT
               E E4+ALL
L15         2332 S E4+NT
L16         2340 S E5
               E E8+ALL
L17         1062 S E4+NT
L18         1531 S E11+NT
               E E11+ALL
L19         1873 S GLYCOPHOSPHOPROTEINS/CT (L) P
L20          837 S GLYCOPROTEINS/CT (L) P
               E DRUG RESISTANCE/CT
               E E3+ALL
L21        26554 S E3+NT
               E E13+ALL
L22         4016 S E2
L23           41 S L5 AND L15-L22
L24            2 S L23 AND L7-L9
L25           25 S L23 AND L18-L20
L26           12 S L15,L16 AND L25
L27           17 S L21,L22 AND L25
L28           17 S L26,L27
L29            2 S L14,L24 AND L28
L30            5 S L14,L24,L29
L31            4 S L30 NOT THROMBOSIS/TI
L32           15 S L28 NOT L31
L33           19 S L31,L32
L34           23 S L23-L32 NOT L33
L35           11 S L34 AND MULTIDRUG (L) RESIST?
L36            6 S L34 AND MDR?
L37           16 S L31,L35,L36
L38           16 S L31,L37
L39           11 S L34 NOT L38
L40            2 S L39 AND (IMMUNOASSAY OR DOXORUBICIN)/TI
L41           18 S L38,L40
               SEL RN

     FILE 'REGISTRY' ENTERED AT 08:30:15 ON 11 APR 2001
L42           46 S E1-E46
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Point of Contact:
Jan [illegible]
Librarian-Physical Sciences
CM1 1E01 Tel: 308-4498

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L43          12 S L42 AND SQL/FA
L44           3 S L43 AND (346 OR 1338 OR 1399)/SQL
L45         266 S ANNEXIN
L46         267 S L44,L45

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L47         138 S L46
L48           2 S L47 AND L5
L49          18 S L41,L48
L50        3013 S L7,L8,L9 OR ANNEXIN OR L47
L51        2070 S L50 AND (PD<=19981026 OR PRD<=19981026 OR AD<=19981026 OR PY<
L52          11 S L51 AND L15-L17,L21,L22
L53           4 S L51 AND MDR?
L54          10 S L51 AND MULTIDRUG (L) RESIST?
L55          12 S L52-L54
L56        2211 S L15-L17,L21,L22 AND L18-L20
L57        2381 S MULTIDRUG (L) RESIST? AND L18-L20
L58        1923 S MDR? AND L18-L20
L59           4 S L56-L58 AND (P40 OR P 40)
L60          16 S L55,L59
L61          12 S L60 NOT L41
                E P-GLYCOPROTEIN/CT
                E E4+ALL
L62        1531 S E11+NT
L63           9 S L5 AND L62
L64           8 S L63 AND L15-L17,L21,L22
L65           8 S L63 AND MULTIDRUG (L) RESIST?
L66           5 S L63 AND MDR?
L67          24 S L41,L64-L66
L68           0 S L63 NOT L67
L69         929 S L62 AND L15-L17,L21,L22
L70        1090 S L62 AND (MULTIDRUG (L) RESIST? OR MDR?)
L71        1162 S L69,L70
L72           4 S L71 AND L51
L73          36 S L60,L61,L67,L72
                E DRUG SCREENING/CT
                E E3+ALL
L74       12105 S E2,E1+NT
                E E7+ALL
L75        3151 S E3
                E E13+ALL
L76        1577 S E5+NT
L77       11320 S E9+NT
L78       63573 S E10+NT
                E TEST KIT/CT
                E E4+ALL
L79        2840 S E2+NT
L80          49 S L51 AND L74-L79
L81         167 S L18-L20,L62 AND L74-L79
L82           2 S L80 AND L81
L83          70 S L15-L17,L21,L22 AND L80,L81
L84          72 S MULTIDRUG(L)RESIS? AND L80,L81
L85          62 S MDR? AND L80,L81
L86          51 S L83-L85 AND (PD<=19981026 OR PRD<=19981026 OR AD<=19981026 OR
L87          84 S L73,L82,L86
L88           6 S L87 AND 9/SC,SX
L89          12 S L87 AND ANNEXIN?
L90           1 S L87 AND P40
L91           5 S L87 AND P 40
L92          18 S L88-L91

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 08:53:04 ON 11 APR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1967 - 11 Apr 2001 VOL 134 ISS 16
FILE LAST UPDATED: 10 Apr 2001 (20010410/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.

=> d bib abs hitrn tot l92

L92 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:824522 HCAPLUS
DN 134:14947
TI Protein-protein interactions and methods for identifying interacting proteins and the amino acid sequence at the site of interaction
IN **Georges, Elias**
PA McGill University, Can.
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000070351	A2	20001123	WO 2000-CA587	20000512

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-134259 19990514
AB The invention relates to protein-protein interactions and methods for identifying interacting proteins and the amino acid sequence at the site of interaction. Using overlapping hexapeptides that encode for the entire amino acid sequences of the linker domains of human P-glycoprotein gene 1 and 3 (HP-gp1 and HP-gp3), a direct and specific binding between P-gp1 and 3 linker domains and intracellular proteins was demonstrated. Three different stretches (617EKGIYFKLVTM627, 658SRSSLIRKRSTRRSVRGSQA677 and 694PVSFWRIMKLNLT706 for P-gp1 and 618LMKKEGVYFKLVNM631, 648KAATRMAPNGWKSRLFRHSTQKNLKNS674 and 695PVSFLKVLKLNKT677 for P-gp3) in linker domains bound to proteins with apparent mol. masses of <<sim80 kDa, 57 kDa and 30 kDa. The binding of the 57 kDa protein was further characterized. Purifn. and partial N-terminal amino acid sequencing of the 57 kDa protein showed that it encodes the N-terminal amino acids of alpha and beta-tubulins. The method of the present invention was further

validated with **Annexin**. The present invention thus demonstrates a novel concept whereby the interactions between two proteins are mediated by strings of few amino acids with high and repulsive binding energies, enabling the identification of high-affinity binding sites between any interacting proteins.

L92 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:262843 HCAPLUS
DN 133:159707
TI Elevated Bcl-2/Bax are a consistent feature of apoptosis resistance in B-cell chronic lymphocytic leukemia and are correlated with in vivo chemoresistance
AU Pepper, Chris; Hoy, Terry; Bentley, Paul
CS Department of Haematology, Llandough Hospital, Penarth, South Glamorgan, UK
SO Leuk. Lymphoma (**1998**), 28(3/4), 355-361
CODEN: LELYEA; ISSN: 1042-8194
PB Harwood Academic Publishers
DT Journal
LA English
AB We investigated the relationship between drug resistance and Bcl-2/Bax in B-cell chronic lymphocytic leukemia (B-CLL). Apoptosis was induced in vitro with chlorambucil and cell death was monitored by dual-labeled FACS anal. using **Annexin** V and propidium iodide. Bcl-2 and Bax protein expression was quantified using FACS and a correlation between drug-induced apoptosis and Bcl-2/Bax was established. Cells were then sorted into viable and nonviable populations according to their forward and side-scatter characteristics and re-analyzed for Bcl-2/Bax. The most resistant cells had elevated Bcl-2 levels and low Bax expression. Furthermore, those cells which were undergoing apoptosis showed only a marginal redn. in Bcl-2 expression, but significantly elevated Bax expression following exposure to chlorambucil. The Bcl-2/Bax was significantly greater in the cell fractions resistant to chlorambucil-induced apoptosis. This observation further supports the suggestion that Bax is the pivotal protein in detg. the fate of cells following apoptotic signals.
RE.CNT 24
RE
(3) Chittenden, T; Nature 1995, V374, P733 HCAPLUS
(7) Holder, M; Eur J Immunol 1993, V23, P2368 HCAPLUS
(8) Jewell, A; Br J Haematol 1994, V88, P268 HCAPLUS
(9) Kitada, S; Antisense Res Dev 1994, V4, P71 HCAPLUS
(10) Korsmeyer, S; Seminars in Cancer Biol 1993, V4, P327 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:176017 HCAPLUS
DN 132:219218
TI Diagnosis of **multidrug resistance** in cancer and infectious lesions using immunoconjugates
IN Goldenberg, David M.
PA Immunomedics, Inc., USA
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000014537	A2	20000316	WO 1999-US20017	19990901 <--
	WO 2000014537	A3	20000720		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GD, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,

MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9957991 A1 20000327 AU 1999-57991 19990901 <--
PRAI US 1998-99304 19980904 <--
WO 1999-US20017 19990901
AB Immunoconjugates of a diagnostic agent and an antibody component that binds an epitope of a **multidrug** transporter protein are disclosed. Thesse immunoconjugates are used in in vivo diagnostic methods to det. whether the failure of traditional chemotherapy is due to the presence of **multidrug resistant** tumor cells, **multidrug resistant** HIV-infected cells or **multidrug resistant** infectious agents.

L92 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:795994 HCAPLUS
DN 132:31744
TI Gene probes used for genetic profiling in healthcare screening and planning
IN Roberts, Gareth Wyn
PA Genostic Pharma Ltd., UK
SO PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI GB 1998-12099 19980606 <--
GB 1998-13291 19980620 <--
GB 1998-13611 19980624 <--
GB 1998-13835 19980627 <--
GB 1998-14110 19980701 <--
GB 1998-14580 19980707 <--
GB 1998-15438 19980716 <--
GB 1998-15574 19980718 <--
GB 1998-15576 19980718 <--
GB 1998-16085 19980724 <--
GB 1998-16086 19980724 <--
GB 1998-16921 19980805 <--
GB 1998-17097 19980807 <--
GB 1998-17200 19980808 <--
GB 1998-17632 19980814 <--
GB 1998-17943 19980819 <--

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and

their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic.RTM." profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L92 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:795993 HCAPLUS
DN 132:31743
TI Gene probes used for genetic profiling in healthcare screening and planning
IN Roberts, Gareth Wyn
PA Genostic Pharma Limited, UK
SO PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9964626	A2	19991216	WO 1999-GB1779	19990604	<--
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
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	AU 9941586	A1	19991230	AU 1999-41586	19990604	<--
	AU 9941587	A1	19991230	AU 1999-41587	19990604	<--
	GB 2339200	A1	20000119	GB 1999-12914	19990604	<--
	EP 1084273	A1	20010321	EP 1999-925207	19990604	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					

PRAI	GB 1998-12098	19980606	<--
	GB 1998-28289	19981223	
	GB 1998-16086	19980724	<--
	GB 1998-16921	19980805	<--
	GB 1998-17097	19980807	<--
	GB 1998-17200	19980808	<--
	GB 1998-17632	19980814	<--
	GB 1998-17943	19980819	<--
	WO 1999-GB1779	19990604	

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to

the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L92 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:299504 HCAPLUS
DN 130:308198
TI Identification of **P-40** as **Annexin** I and its role in **multidrug resistance**
IN **Georges, Elias; Wang, Ying**
PA McGill University, Can.
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9921980	A1	19990506	WO 1998-CA992	19981026 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2219299	AA	19990424	CA 1997-2219299	19971024 <--
AU 9896174	A1	19990517	AU 1998-96174	19981026 <--
EP 1025225	A1	20000809	EP 1998-949842	19981026 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI CA 1997-2219299 19971024 <--
WO 1998-CA992 19981026 <--

AB The invention identifies **P-40** as **Annexin** I, a member of a large family of calcium-dependent phospholipid binding proteins implicated in intracellular membrane vascular trafficking and exocytosis processes. The overexpression of **P-40** alone or together with P-glycoprotein (P-gp) or the **multidrug resistance** assocd. protein (MRP) in **MDR** cell lines has been previously reported, but this invention is the first to show the role of **Annexin** I (**P-40**) overexpression in the **resistance** of tumor cells to Taxol and adriamycin, the identification of its gene as a member of the **MDR** gene family, and the existence of an **Annexin**-based **multidrug resistance** pathway. Also provided is a method of reducing **Annexin**-based **MDR** in a cell or animal, comprising the step of administering a therapeutically effective amt. of a pharmaceutical compn. according to the invention.

IT **101963-61-5**, Lipocortin (human clone .lambda.L4-211 protein moiety reduced)
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(amino acid sequence; identification of **P-40** as **Annexin** I and its role in **multidrug resistance**)

IT **139808-63-2**, GenBank X05908
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; identification of **P-40** as **Annexin** I and its role in **multidrug**

resistance)
RE.CNT 6
RE
(2) Biogen Nv; WO 8604094 A 1986 HCAPLUS
(3) Carollo, M; ONCOLOGY RESEARCH 1998, V10(5), P245 HCAPLUS
(4) Cole, S; BRITISH JOURNAL OF CANCER 1992, V65(4), P498 HCAPLUS
(5) Horseman, N; GENERAL AND COMPARARTIVE ENDOCRINOLOGY 1992, V85(3), P405 HCAPLUS
(6) Wang, Y; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1997, V236(2), P483 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:130617 HCAPLUS
DN 130:191863
TI Methods of identifying biological agent compositions using segmented copolymers
IN Kabanov, Alexander V.; Alakov, Valery Y.; Pietrzynski, Grzegorz Jerzy
PA Supratek Pharma Inc., Can.
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9908112	A1	19990218	WO 1998-US16300	19980805 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9888981	A1	19990301	AU 1998-88981	19980805 <--
EP 1005651	A1	20000607	EP 1998-940788	19980805 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1997-55256 19970808 <--
US 1998-47109 19980324 <--
WO 1998-US16300 19980805 <--
AB New methods of identifying biol. agent compns. involving (a) prepg. a plurality of segmented copolymers, the segmented copolymers differing in at least one of the following, (i) at least one of their segment lengths, (ii) chem. structure, (iii) copolymer architecture; (b) prepg. compns. of the segmented copolymers with a biol. agent; (c) testing at least one of the compns. of segmented copolymers with a biol. agent for biol. properties using a cell, animal, plant or other biol. model, or measurement of a chem. or phys. property in a test tube, or a theor. model; and (d) identifying the compns. with desired biol. properties. The invention is designed to reduce the time and cost for creating desired drug compds. which are not only immediately ready for clin. trials, but also possess a no. of important characteristics increasing the probability of the ultimate success. Unlike combinatorial chem., the invention does not discover new drug structures or alter the desirable drug's characteristics, but instead provides optimal compns. of a desired drug, solving the drug's problems of soly., bioavailability, resistance to metabolic enzymes, toxicity, membrane transport, site specific delivery, etc.
RE.CNT 6
RE
(1) Kabanov, A; FEBS 1989, V258(2), P343 HCAPLUS
(2) Kabanov, A; Macromolecules 1995, V28, P2303 HCAPLUS
(3) Katayose, S; Proceed Intern Symp Control Rel Bioact Mater 1996, V23, P899
(4) Sundberg; US 5624711 A 1997

(5) Vinogradov, S; Bioconjugate Chem 1996, V7, P3 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:52622 HCAPLUS
DN 130:232089
TI Membrane fluidization by ether, other anesthetics, and certain agents abolishes P-glycoprotein ATPase activity and modulates efflux from **multidrug-resistant** cells
AU Regev, Ronit; Assaraf, Yehuda G.; Eytan, Gera D.
CS Department of Biology, Technion-Israel Institute of Technology, Haifa, 32000, Israel
SO Eur. J. Biochem. (1999), 259(1/2), 18-24
CODEN: EJBCAI; ISSN: 0014-2956
PB Blackwell Science Ltd.
DT Journal
LA English
AB The anesthetics benzyl alc. and the nonarom. chloroform and di-Et ether, abolish P-glycoprotein (Pgp) ATPase activity in a mode that does not fit classical competitive, noncompetitive, or uncompetitive inhibition. At concns. similar to those required for inhibition of ATPase activity, these anesthetics fluidize membranes leading to twofold acceleration of doxorubicin flip-flop across lipid membranes and prevent photoaffinity labeling of Pgp with [125I]-iodoarylazidoprazosin. Similar concns. of ether proved nontoxic and modulated efflux from Pgp-overexpressing cells. A similar twofold acceleration of doxorubicin flip-flop rate across membranes was obsd. with neutral mild detergents, including Tween 20, Nonidet **P-40** and Triton X-100, and certain Pgp modulators, such as verapamil and progesterone. Concns. of these agents, similar to those required for membrane fluidization, inhibited Pgp ATPase activity in a mode similar to that obsd. with the anesthetics. The mode of inhibition, i.e. lack of evidence for classical enzyme inhibition and the correlation of Pgp ATPase inhibition with membrane fluidization over a wide range of concns. and structures of drugs favors the direct inhibition of Pgp ATPase activity by membrane fluidization. The unusual sensitivity of Pgp to membrane fluidization, as opposed to acceleration of ATPase activity of ion transporters, could fit the proposed function of Pgp as a "flippase", which is in close contact with the membrane core.
RE.CNT 53
RE
(1) al-Shawi, M; J Biol Chem 1993, V268, P4197 HCAPLUS
(3) Ayesh, S; Biochim Biophys Acta 1996, V1316, P8 HCAPLUS
(4) Bates, S; Stem Cells 1996, V14, P56 HCAPLUS
(5) Beck, W; Cancer Res 1996, V56, P3010 HCAPLUS
(6) Borgnia, M; J Biol Chem 1996, V271, P3163 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:806296 HCAPLUS
DN 130:204754
TI 2-Deoxy-D-glucose preferentially kills **multidrug-resistant** human KB carcinoma cell lines by apoptosis
AU Bell, S. E.; Quinn, D. M.; Kellett, G. L.; Warr, J. R.
CS Department of Biology, The University of York, York, YO10 5YW, UK
SO Br. J. Cancer (**1998**), 78(11), 1464-1470
CODEN: BJCAAI; ISSN: 0007-0920
PB Churchill Livingstone
DT Journal
LA English
AB The aim of this study was to det. the mechanism of cell death assocd. with the preferential killing of **multidrug-resistant** (**MDR**) cells by the glycolytic inhibitor 2-deoxy-D-glucose (2DG) in a range of **MDR** human KB carcinoma cell lines selected in different drugs. The D10 values for KB-V1, KB-C1 and KB-A1 (selected in vinblastine, colchicine and doxorubicin, resp.) were 1.74, 1.04 and 0.31 mM, resp., compared with 4.60 mM for the parental cell line (KB-3-1). The

mechanism of cell death was identified as apoptosis, based on nuclear morphol., **annexin** V binding and poly(ADP-ribose) polymerase (PARP) cleavage. 2DG induced apoptosis in the three **MDR** cell lines in a dose- and time-dependent manner and did not induce necrosis. PARP cleavage was detected in KB-C1 cells within 2 h of exposure to 50 mM 2DG and slightly later in KB-A1 and KB-V1 cells. The relative levels of 2DG sensitivity did not correlate with the levels of **multidrug resistance** or with the reduced levels of the glucose transporter GLUT-1 in these cells. The authors speculate that a 2DG-stimulated apoptotic pathway in **MDR** KB cells differs from that in normal KB cells.

RE.CNT 31
RE
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(2) Bellamy, W; Adv Clin Chem 1994, V31, P1 HCAPLUS
(3) Bentley, J; Oncol Res 1996, V8, P77 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:723036 HCAPLUS
DN 130:179468
TI Increased expression of **annexin** I and thioredoxin detected by two-dimensional gel electrophoresis of drug resistant human stomach cancer cells
AU Sinha, Pranav; Hutter, Gero; Kottgen, Eckart; Dietel, Manfred; Schadendorf, Dirk; Lage, Hermann
CS Campus Virchow-Klinikum, Institut fur Laboratoriumsmedizin und Pathobiochemie, Universitatsklinikum Charite, Berlin, Germany
SO J. Biochem. Biophys. Methods (**1998**), 37(3), 105-116
CODEN: JBBMDG; ISSN: 0165-022X
PB Elsevier Science B.V.
DT Journal
LA English
AB The therapy of advanced cancer using chemotherapy alone or in combination with radiation or hyperthermia yields an overall response rate of about 20-50%. This success is often marred by the development of **resistance** to cytostatic drugs. Our aim was to study the global anal. of protein expression in the development of chemoresistance in vitro. We therefore used a cell culture model derived from the gastric carcinoma cell line EPG 85-257P. A classical **multidrug-resistant** subline EPG85-257RDB selected to daunorubicin and an atypical **multidrug-resistant** cell variant EPG85-257RNOV selected to mitoxantrone, were analyzed using two-dimensional electrophoresis in immobilized pH-gradients (pH 4.0-8.0) in the first dimension and linear polyacrylamide gels (12%) in the second dimension. After staining with Coomassie brilliant blue, image anal. was performed using the PDQuest system. Spots of interest were isolated using preparative two-dimensional electrophoresis and subjected to microsequencing. A total of 241 spots from the EPG85-257RDB-std. and 289 spots from the EPG85-257RNOV-std. could be matched to the EPG85-257P-std. Microsequencing after enzymic hydrolysis in gel, mass spectrometric data and sequencing of the peptides after their fractionation using microbore HPLC identified that two proteins **annexin** I and thioredoxin were overexpressed in chemoresistant cell lines. **Annexin** I was present in both the classical and the atypical **multidrug-resistant** cells. Thioredoxin was found to be overexpressed only in the atypical **multidrug-resistant** cell line.

RE.CNT 43
RE
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:716631 HCAPLUS
DN 130:119718
TI Dexamethasone-induced cytotoxic activity and drug resistance effects in androgen-independent prostate tumor PC-3 cells are mediated by lipocortin 1
AU Carollo, Maria; Parente, Luca; D'Alessandro, Natale
CS Institute of Pharmacology, Faculty of Medicine and tPharmacy, University of Palermo, Italy
SO Oncol. Res. (**1998**), 10(5), 245-254
CODEN: ONREE8; ISSN: 0965-0407
PB Cognizant Communication Corp.
DT Journal
LA English
AB We have examd. the effects that dexamethasone (DEX), alone or in combination with doxorubicin (DOX), cisplatin (CDDP), or etoposide (VP-16), exerts on the growth of the androgen-independent prostate cancer PC-3 cells. DEX exhibited only a limited cytotoxicity (growth inhibition of about 28% or 20% after 24 or 72 h of exposure, resp. in the range of DEX 10-100 nM) and did not induce apoptosis in the cells. This cytotoxicity of DEX was mimicked by an active peptide (peptide Ac2-26) drawn from the human lipocortin 1 N-terminus region and abrogated by an antibody to human lipocortin 1. Two inhibitors of arachidonic acid metab., tenidap and indomethacin, also caused cytotoxicity. The cytotoxic effects of DEX in combination with DOX, CDDP, or VP-16 were antagonistic when the steroid was administered 3 h before or simultaneously with the drugs. Other schedule-dependency expts. further clarified that, at least in the case of the combination with DOX. it is the steroid that desensitizes the cells to the drug. When peptide Ac2-26, tenidap, or indomethacin were tested in combination with DOX, antagonism was also obsd. DEX treatment neither modified the ability of the cells to accumulate DOX nor changed their weak expression of P-glycoprotein. PC-3 cells also produce IL-6, which autocrinally stimulates their growth, and whose gene expression may be reduced by glucocorticoids. In the present expts. DEX only slightly decreased the prodn. and secretion of IL-6 by the cells. The present findings suggest that the slight cytotoxic activity and the drug resistance effects of DEX on PC-3 cells are mediated by induction of lipocortin 1 and inhibition of arachidonic acid metab., with no relationship to downregulation of IL-6 levels. These findings indicate also that the combination of DEX with conventional chemotherapeutic agents may result in antagonistic antitumor effects.
RE.CNT 49
RE
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(2) Almawi, W; J Immunol 1996, V157, P5231 HCAPLUS
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(4) Black, K; Endocrinology 1991, V128, P2657 HCAPLUS
(5) Borner, M; Cancer Res 1995, V55, P2122 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:352961 HCAPLUS
DN 129:37202
TI Novel polymeric complexes for the transfection of nucleic acids, with residues causing the destabilization of cell membranes
IN Midoux, Patrick; Monsigny, Michel
PA I.D.M. Immuno-Designed Molecules, Fr.; Midoux, Patrick; Monsigny, Michel
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 9822610 A1 19980528 WO 1997-FR2022 19971110 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
FR 2755976 A1 19980522 FR 1996-13990 19961115 <--
FR 2755976 B1 19990115
AU 9851239 A1 19980610 AU 1998-51239 19971110 <--
EP 946744 A1 19991006 EP 1997-945903 19971110 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 2001504344 T2 20010403 JP 1998-523257 19971110 <--
PRAI FR 1996-13990 19961115 <--
WO 1997-FR2022 19971110 <--
OS MARPAT 129:37202
AB The invention concerns a complex between at least a (neg. charged) nucleic acid and at least a pos. charged polymeric conjugate, the bond between the nucleic acid and the polymeric conjugate being electrostatic in nature, the polymeric conjugate contg. a polymer formed by monomer units bearing free NH3+ functions, and being such that: the free NH3+ functions of said monomer units are substituted in a ratio of .gtoreq.10 % by residues causing in weak acid medium destabilization of cell membranes, in particular the endocytosis vesicle membrane, and/or endosomes; said residues having further the following properties: they comprise a functional group for being fixed to said polymer, they are not active as recognition signal identified by a cell membrane receptor, they can comprise at least one free NH3+ function; said uncharged residues having further the following properties: they comprise at least a hydroxyl group, they are not active as recognition signal identified by a cell membrane receptor, the hydroxyl groups of said uncharged residues being capable of being substituted by at least a mol. which constitutes a recognition signal identified by a cell membrane receptor, with reservation that the whole set of free NH3+ functions is at least 30 % of the no. of monomer units of the polymeric network of said polymeric conjugate.

L92 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:221998 HCAPLUS
DN 128:289870
TI Short course infusional idarubicin plus intermittent cytarabine and etoposide for refractory hematologic malignancies: clinical and preliminary pharmacological results
AU Bassan, Renato; Chiodini, Barbara; Zucchetti, Massimo; Lerede, Teresa; Cornelli, Pier Emilio; Cortelazzo, Sergio; Barbui, Tiziano
CS Div. Ematologia and Pediatria, Ospedali Riuniti, Bergamo, Italy
SO Haematologica (**1998**), 83(1), 27-33
CODEN: HAEMAX; ISSN: 0390-6078
PB Il Pensiero Scientifico Editore
DT Journal
LA English
AB Idarubicin (IDA) is relatively immune to the **multidrug resistance** P-gp mechanism that is frequently expressed in recurrent and refractory hematol. malignancies. Owing to rapid metab. in vivo, a continuous infusion (CI) of IDA might prolong exposure time to the parent drug rather than its more P-gp susceptible alc. metabolite. For this reason we developed a brief retreatment schedule incorporating CI IDA in order to obtain clin. as well as preliminary pharmacol. data in patients with refractory leukemias and lymphomas. Eligible patients had either advanced-stage acute myeloid or lymphoid leukemias (AML, ALL) or high-grade non-Hodgkin's lymphomas (NHL) which failed curative-intent front-line or salvage regimens in use at our institution during the study period (July-Oct. 1992). CI IDA 5 mg/m2/d was employed together with intermittent (every 8 h) intermediate-dose cytarabine (500 mg/m2) and

etoposide (200 mg/m2); all drugs were given for 2-4 days. A preliminary pharmacokinetic evaluation of CI IDA was carried out in three patients, including a comparison with bolus delivery in one. The in vitro effects of CI-type vs bolus-type IDA delivery in terms of intracellular IDA accumulation and related pro-apoptotic activity were assessed in P-gp- and P-gp+ human leukemic CEM cells by means of cytofluorimetry (IDA fluorescence intensity = FI, **annexin** V expression), with and without the addn. of P-gp inhibitor cyclosporin A (CsA). Complete (2) or partial (4) responses were achieved in a total of 12 patients (17% and 33%, resp.), despite prior treatments with anthracyclines (100% of cases) and cytarabine-etoposide (33% of cases). Hematol. toxicity caused the duration of treatment to be reduced from 4 days to 2 days after the first 4 patients. The procedural death rate was 42% (5/12), which was probably related in part to the sum of adverse prognostic characteristics: median patient age 55 yr, two-thirds of cases having previously failed second/third-line regimens. The pharmacokinetic study showed an increased plasma AUC value with CI IDA in one patient (2.9-fold increase vs bolus delivery) due to the prolonged presence of low IDA plasma levels (10-20 ng/mL vs 50 ng/mL), as seen in two other cases as well. On the other hand, the in vitro study did not prove to be in favor of CI IDA because the FI threshold (>1500 units) assocd. with increased apoptosis of P-gp+ cells (>10%) was achieved only with bolus-type IDA exposure (50 ng/mL for 30') plus CsA. This short regimen demonstrated activity against end-stage leukemias and lymphomas and might prove to be more effective and less toxic in younger patients and in those with less advanced disease. In view of the results from plasma pharmacokinetics and in vitro intracellular IDA accumulation and apoptosis assays in lymphoblastic CEM cells, CI IDA 5 mg/m2/day may not represent a better therapeutic option than a rapid bolus injection, particularly in P-gp+ neoplasms. If obtaining an adequate intracellular drug concn. is the primary treatment goal, a higher CI IDA dosage, the addn. of a P-gp down-regulator such as CsA and others, and an in vivo study focusing on tumor samples from patients could all be helpful.

L92 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:26639 HCAPLUS
DN 128:136189
TI Idarubicin activity against **multidrug-resistant** (**mdr**-1+) cells is increased by cyclosporin A
AU Chiodini, B.; Bassar, R.; Borleri, G.; Lerede, T.; Barbui, T.
CS Haematology Dep., Ospedali Riuniti, Bergamo, Italy
SO Haematol. Blood Transfus. (**1998**), 39(Acute Leukemias VII), 475-482
CODEN: HBTRDV; ISSN: 0171-7111
PB Springer-Verlag
DT Journal
LA English
AB **Multidrug resistance** related to functional overexpression of P-170 glycoprotein (**mdr**-1 gene) is often responsible for treatment failure in acute leukemia. Attempts to restore drug sensitivity with revertants and less vulnerable drugs are underway. We compared the ability of cyclosporin A to modulate **mdr**-1 **resistance** of T-lymphoblastic CEM cells to daunorubicin and idarubicin. To obtain clin. useful informations, exptl. conditions reproduced partially in vivo pharmacol. (drug peak plasma levels, alc. metabolites, exposure times) of a single i.v. bolus with daunorubicin 45 mg/m2 or idarubicin 10-12 mg/m2, plus cyclosporin A 16 mg/kg/d given as continuous infusion (List schedule). Study methods were cytofluorimetry for detection of anthracycline early uptake, retention and pro-apoptotic effects (binding to fluoresceinated **annexin** V) at the single cell level, and the std. MTT growth inhibition assay for cytotoxicity. The results showed greater drug uptake/retention and apoptotic rates with idarubicin than with daunorubicin, with a further increase by cyclosporin A. MTT results were in favor of idarubicin with or without cyclosporin A, and greatly influenced by cyclosporin A itself. Altogether, study results in **mdr**-1+ cells with idarubicin/idarubicinol at 100/20 ng/mL,

corresponding to levels achievable in vivo with a single idarubicin dose .gtoreq. 12 mg/m2, were in the range of those obtained with std.-dose daunorubicin in **mdr**-1-cells. These findings underscore the potential usefulness of an idarubicin plus cyclosporin A combination in **mdr**-1+ leukemias, and prompt further studies on assocns. with other modulators of P-170 functional activity.

L92 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:482094 HCAPLUS
DN 127:188961
TI Overexpression of a 40-kDa protein in human **multidrug resistant** cells
AU **Wang, Ying**; Pan, Xing-Qing; Lheureux, Francoise; **Georges, Elias**
CS Institute of Parasitology, McGill University, Ste-Anne de Bellevue, PQ, H9X 3V9, Can.
SO Biochem. Biophys. Res. Commun. (1997), 236(2), 483-488
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
AB The use of anticancer drugs in the chemotherapeutic treatment of cancer patients frequently results in the emergence of drug **resistant** tumors. Selection of tumor cell lines in vitro has led to the identification of several proteins that mediate drug **resistance** to anticancer drugs. In this study, an immuno-dot blot method was used to isolate a monoclonal antibody (IPM96) which recognized a 40 kDa protein (or **P-40**) co-expressed with P-glycoprotein and MRP in several **multidrug resistant** cell lines (MCF-7/Adr, SKOV/VLB1.0, H69/Adr, and HL60/AR). Furthermore, **P-40** levels dropped significantly in one revertant cell line (H69/PR) derived from H69/AR cells. Interestingly, the expression of **P-40** was also higher in two tumor cell lines (SKTax6a and A2780CP) that were selected with paclitaxel or cisplatin but do not express P-gp or MRP. Immuno-fluorescence staining of cells with IPM96 showed both membrane and cytoplasmic staining. These results were confirmed by Western blot anal. of different subcellular fractions from MCF-7/Adr cells. The membrane bound **P-40** was **resistant** to extn. with high salt, chelating agents, and denaturing agents, but was solubilized with 10 mM CHAPS. The overexpression of **P-40** in **multidrug resistant** cells has not been previously detd. and therefore could be important in the expression of the drug **resistance** phenotype.

L92 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:124296 HCAPLUS
DN 120:124296
TI Interaction of **multidrug-resistant** Chinese hamster ovary cells with amphiphiles
AU Loe, D.W.; Sharom, F.J.
CS Guelph-Waterloo Cent. Grad. Work Chem., Univ. Guelph, Guelph, ON, N1G 2W1, Can.
SO Br. J. Cancer (1993), 68(2), 342-351
CODEN: BJCAAI; ISSN: 0007-0920
DT Journal
LA English
AB The interaction of membrane-active amphiphiles with a series of **MDR** Chinese hamster ovary (CHO) cell lines was investigated. Cross-resistance to cationic amphiphiles was obsd., which was effectively sensitized by verapamil. **MDR** cells showed collateral sensitivity to polyoxyethylene amphiphiles (Triton X-100/Nonidet **P-40**), which reached a max. at 9-10 ethylene oxide units. Resistant lines were also highly collaterally sensitive (17-fold) to dibutylphthalate. **Mdr1** transfectants showed cross-resistance to cationic amphiphiles, but no collateral sensitivity to nonionic species. Triton X-100/Nonidet **P-40** inhibited 3H-azidopine

photoaffinity labeling at low concns., perhaps reflecting a specific interaction with P-glycoprotein. Further investigation of the mol. basis of collateral sensitivity revealed that assocn. of 3H-Triton X-100 with **MDR** cells reached steady state levels rapidly, and occurred by a non-mediated mechanism. The equil. level of X-100 uptake was inversely related to drug resistance. Collateral sensitivity is thus not a result of decreased Triton X-100 assocn. with the cell. The fluorescent probe merocyanine 540 was used to examine the **MDR** plasma membrane microenvironment for physicochem. changes. Increasing levels of drug resistance correlated with a progressive shift in the mean cell fluorescence to lower levels, which suggests that the packing d. in the outer leaflet of **MDR** cells is increased relative to that of the drug-sensitive parent.

L92 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:94968 HCAPLUS
DN 120:94968
TI Effects of nonionic detergents on P-glycoprotein drug binding and reversal of **multidrug resistance**
AU Zordan-Nudo, Tracy; Ling, Victor; Liu, Zhi; **Georges, Elias**
CS Inst. Parasitol., McGill Univ., Montreal, PQ, H9X 1C0, Can.
SO Cancer Res. (1993), 53(24), 5994-6000
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB **Multidrug-resistant** cells are thought to maintain low intracellular cytotoxic drug concn. though the active efflux of drugs across the cell membrane. It is presently believed that P-glycoprotein mediates this energy-dependent drug efflux by interacting directly with various lipophilic compds. In this report, [3H]azidopine was used in a photoaffinity labeling assay to study the effect of detergents and denaturing agents on drug binding by P-glycoprotein in intact lymphoma cells. Nonionic detergents such as Triton X-100 or Nonidet **P-40** at very low concns. completely abolished azidopine photolabeling of P-glycoprotein and were able to reverse the **multidrug resistance** phenotype. In contrast, high concns. of the denaturing agent urea or the zwitterionic detergent 3-[(3-cholamidopropyl)dimethylamino]-1-propanesulfonate did not inhibit azidopine photolabeling of P-glycoprotein. A comparison between verapamil and Triton X-100 revealed that the latter was the more effective in inhibiting azidopine photolabeling of P-glycoprotein, while verapamil was the more effective in potentiating [3H]vinblastine accumulation in drug-**resistant** cells. Drug transport studies showed that [3H]Triton X-100 accumulated in both drug-sensitive and -**resistant** cells, and its accumulation was not modulated by excess vinblastine, verapamil, or colchicine. These findings suggest that low concns. of Triton X-100 reverse the **multidrug resistance** phenotype by inhibiting drug binding by P-glycoprotein. It is also suggested that the site(s) of drug binding by P-glycoprotein is localized to sequences within the lipid bilayer of the cell membrane.

L92 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:420074 HCAPLUS
DN 117:20074
TI Elevated expression of **annexin** II (lipocortin II, p36) in a **multidrug resistant** small cell lung cancer cell line
AU Cole, S. P. C.; Pinkoski, M. J.; Bhardwaj, G.; Deeley, R. G.
CS Cancer Res. Lab., Queen's Univ., Kingston, ON, K7L 3N6, Can.
SO Br. J. Cancer (**1992**), 65(4), 498-502
CODEN: BJCAAI; ISSN: 0007-0920
DT Journal
LA English
AB The doxorubicin-selected **multidrug resistant** small cell lung cancer cell line, H69AR, is cross-**resistant** to the Vinca alkaloids and epipodophyllotoxins, but does not overexpress P-glycoprotein, a 170 kDa plasma membrane efflux pump usually assocd. with

this type of **resistance**. Monoclonal antibodies were raised against the H69AR cell line and one of these, MAb 3.186, recognizes a peptide epitope on a 36 kDa phosphorylated protein that is membrane assocd., but not presented on the external surface of H69AR cells (Mirski & Cole, 1991). Here, in vitro translation and mol. cloning techniques were used to det. the relative levels of mRNA corresponding to the 3.186 antigen. In addn., a cDNA clone contg. an insert of approx. 1.4 kb was obtained by screening an H69AR cDNA library with 125I-MAb 3.186. Fragments of this cloned DNA hybridized to a single mRNA species of approx. 1.6 kb that was 5-6-fold elevated in H69AR cells. Partial DNA sequencing and restriction endonuclease mapping revealed identity of the cloned DNA with p36, a member of the **annexin**/lipocortin family of Ca2+ and phospholipid binding proteins.

=> d bib abs hitrn tot

L108 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:186025 HCAPLUS
TI Gene expression marker nucleic acids and proteins for identification, assessment, prevention, and therapy of ovarian cancer
IN Lee, John; Thompsho, Pamela; Lillie, James
PA Millennium Predictive Medicine, Inc., USA
SO PCT Int. Appl., 1198 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001018542	A2	20010315	WO 2000-US24199	20000901

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-152547 19990903
US 2000-190347 20000316
US 2000-191321 20000321
US 2000-208382 20000531
US 2000-220467 20000720

AB The invention relates to compns., kits, and methods for detecting, characterizing, preventing, and treating human ovarian cancers. A variety of markers are provided, wherein changes in the levels of expression of one or more of the markers is correlated with the presence of ovarian cancer. The level of expression of the marker in a sample can be assessed, for example, by detecting the presence in the sample of: (1) a protein corresponding to the marker or a fragment of the protein using a reagent, such as an antibody or antibody deriv. or fragment, which binds specifically with the protein; (2) a transcribed polynucleotide (e.g., an mRNA or cDNA) having at least a portion with which the marker is substantially homologous by contacting a mixt. of transcribed polynucleotides obtained from the sample with ha substrate having one or more of the markers provided; (3) a transcribed polynucleotide, wherein the polynucleotide anneals with the marker under stringent hybridization conditions. [This abstr. record is one of several records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].
IT **133924-59-1**, GenBank D00017 **139808-63-2**, GenBank X05908
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; gene expression marker nucleic acids and proteins

for identification, assessment, prevention, and therapy of ovarian cancer)

L108 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:115403 HCAPLUS
DN 134:159878
TI Immunoassays for **annexins** and autoantibodies as markers for cancer
IN Hanash, Samir M.; Misek, David; Hinderer, Robert; Beer, David; Brichory, Franck
PA The Regents of the University of Michigan, USA
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001011372	A1	20010215	WO 2000-US21514	20000804

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-370337 19990806
AB The present invention relates to screening methods for diagnosis, prognosis, or susceptibility to cancer in a subject by means of detecting the presence of serum autoantibodies to specific **annexin** protein antigens in sera from subjects. The present invention also provides screening methods for diagnosis and prognosis of cancer in a subject by means of detecting increased expression levels of **annexin** proteins in biol. samples of the subject. The method of the invention can also be used to identify subjects at risk for developing cancer. The method of the invention involves the use of subject derived biol. samples to det. the occurrence and level of expression of **annexin** proteins or expression of **annexin** derived peptides or antigens, and/or the occurrence and level of circulating autoantibodies to specific **annexin** protein antigens. The present invention further provides for kits for carrying out the above described screening methods. Such kits can be used to screen subjects for increased levels of **annexin** proteins, or for the detection of autoantibodies to **annexin** proteins, as a diagnostic, predictive or prognostic indicator of cancer.
RE.CNT 7
RE
(1) Davis, R; JOURNAL OF IMMUNOLOGICAL METHODS 1995, V188(1), P91 HCAPLUS
(2) Kraus, M; US 5316915 A 1994 HCAPLUS
(3) Misek, D; WO 9900671 A 1999 HCAPLUS
(4) Pencil, S; CLINICAL & EXPERIMENTAL METASTASIS 1998, V16(2), P113 HCAPLUS
(5) Pro Duct Health Inc; WO 0039557 A 2000 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:824512 HCAPLUS
DN 134:2315
TI Methods, pharmaceutical formulations and kits for identification of subjects at risk for cancer and for the prevention of cancer in at-risk subjects
IN Neely, Constance F.
PA Link Technology, Inc., USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000070341	A2	20001123	WO 2000-US13102	20000512

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-134276 19990514
AB Subjects at risk for developing cancer may be identified by obtaining samples of diagnostic cells from the subjects and detg. a measure of cytotoxicity of the cells, the measure of cytotoxicity correlating neg. with the risk of developing cancer. The development of cancer may be prevented in subjects detd. to be at risk for developing cancer by administering priming and activating agents to the subject, by increasing the expression of A1 adenosine receptors in cells of the subject, and increasing the affinity of cells of the subject for A1 adenosine receptor ligands. The preventative and diagnostic methods of the present invention may be carried out with kits and pharmaceutical liposomal formulations.

L108 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:646238 HCAPLUS
DN 133:219806
TI Determination of the chemosensitivity via phosphatidyl serine markers
IN Meyer-Almes, Franz Josef
PA Evotec Analytical Systems G.m.b.H., Germany
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000054048	A1	20000914	WO 2000-EP2161	20000311

W: JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

DE 19910955	A1	20000928	DE 1999-19910955	19990312

PRAI DE 1999-19910955 19990312
EP 1999-108496 19990430
AB The invention relates to a method for detg. the chemosensitivity of cells vis-a-vis at least one substance by measuring the level of apoptosis induced by the at least one substance. According to the inventive method, the cells are incubated simultaneously with a cytostatic agent and at least one marker whose interaction with phosphatidyl serine can be detected and the interaction between the marker and the phosphatidyl serine is detected after a certain period of time. Thus blood or bone marrow cells were incubated with the phosphatidyl serine marker **Annexin** V-Alexa 568, BOBO dye, and various antitumor agents, e.g. actinomycin D in a culture medium, contg. calcium. Apoptotic and necrotic cells were quantified based on their different colors via fluorescence microscopy. The method can also be used to det. the effect of environmental toxic substances on cells.
RE.CNT 3
RE
(1) Boersma; CYTOMETRY 1997, V27(3), P275 HCAPLUS
(2) Kravtsov; BLOOD 1998, V92(3), P968 HCAPLUS
(3) Toh, H; LEUKEMIA AND LYMPHOMA 1998, V31(1-2), P195 MEDLINE

L108 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:314867 HCAPLUS
DN 132:344078
TI A system for cell-based screening by using a protease biosensor and its use in drug discovery
IN Guiliano, Kenneth A.; Bright, Gary; Olson, Keith; Burroughs-Tencza, Sarah
PA Cellomics, Inc., USA
SO PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000026408	A2	20000511	WO 1999-US25431	19991029
WO 2000026408	A3	20000914		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-106308 19981030
US 1999-136078 19990526

AB The present invention provides systems, methods, screens, reagents and kits for optical system anal. of cells to rapidly det. the distribution, environment, or activity of fluorescently labeled reporter mols. in cells for the purpose of screening large nos. of compds. for those that specifically affect particular biol. functions. The method comprises using the cells contg. fluorescent reporter mols. in an array of locations; treating the cells with reagents; imaging numerous cells in each location with fluorescence optics; converting the optical information into digital data; and analyzing and interpreting the data. A protease (e.g. caspase) biosensor for the method comprises a recombinant DNA encoding a polypeptide signal (e.g. a fluorescent protein), a protease recognition site, a reactant target sequence is provided to identify the compds. that modify protease activity in cells is provided. A genetically engineered host cell that has been transfected with the recombinant protease biosensor expression vector is also described.

IT **269051-19-6P**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; a system for cell-based screening by using a protease biosensor and use in drug discovery)

IT **269050-95-5P**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; of caspase-3 biosensor; a system for cell-based screening by using a protease biosensor and use in drug discovery)

IT **269051-18-5P 269051-26-5P**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(nucleotide sequence; a system for cell-based screening by using a protease biosensor and use in drug discovery)

IT **269051-36-7**
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(nucleotide sequence; a system for cell-based screening by using a protease biosensor and use in drug discovery)

IT **269051-14-1P**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(nucleotide sequence; for bi-functional caspase-3/cytoskeleton biosensor; a system for cell-based screening by using a protease biosensor and use in drug discovery)
IT **269050-94-4P**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(nucleotide sequence; for caspase-3 biosensor; a system for cell-based screening by using a protease biosensor and use in drug discovery)

L108 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:241284 HCAPLUS
DN 132:290755
TI Chemical structure with affinity for a phospholipid, and marker compound, diagnosis kit, and medicine comprising said structure
IN Sanson, Alain; Russo-Marie, Francoise; Neumann, Jean-Michel; Cordier-Ochsenbein, Francoise; Guerois, Raphael
PA Commissariat a l'Energie Atomique, Fr.; Universite Pierre et Marie Curie (Paris VI)
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000020453	A1	20000413	WO 1999-FR2329	19990930 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2784106	A1	20000407	FR 1998-12366	19981002 <--
AU 9958694	A1	20000426	AU 1999-58694	19990930 <--
PRAI FR 1998-12366	19981002 <--			
WO 1999-FR2329	19990930			

OS MARPAT 132:290755
AB The invention concerns a compd. with affinity for a neg. charged phospholipid and a detection mol., a conjugate and a pharmaceutical compn. contg. said compd. Generally speaking, the compd. of the invention is useful for specific recognition of lipid vectors and can be used for engineering and prepg. compds. for identifying and sequestering neg. charged lipids, such as phosphatidyl serine and phosphatidic acid. Said chem. structure many be a cyclic peptide structure or **annexin** domain. These compds. may be used to prep. antithrombotics, antitumor agents, and inflammation inhibitors.
IT **101963-61-5**, **Annexin** I (human) **264119-09-7**, **Annexin** V (human) **264119-10-0**, **Annexin** III (human) **264119-11-1**, **Annexin** IV (human)
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(amino acid sequence; phospholipid-binding cyclic compds. for diagnostic kits)
RE.CNT 16
RE
(1) Cordier-Ochsenbein, F; J MOL BIOL 1998, V279, P1163 HCAPLUS
(2) Cordier-Ochsenbein, F; J MOL BIOL 1998, V279, P1163 HCAPLUS
(3) Ernst, J; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1994,

V200(2), P867 HCAPLUS
(4) Ernst, J; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1994, V200(2), P867 HCAPLUS
(7) Macquaire, F; BIOCHEMISTRY 1993, V32, P7244 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:819571 HCAPLUS
DN 132:59136
TI High-throughput methods, systems and apparatus for performing cell-based screening assays
IN Wada, H. Garrett; Sundberg, Steven A.; Alajoki, Marja Liisa
PA Caliper Technologies Corp., USA
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9967639	A1	19991229	WO 1999-US13918	19990621 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9949570	A1	20000110	AU 1999-49570	19990621 <--
EP 1088229	A1	20010404	EP 1999-933529	19990621 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1998-104519 19980625 <--
US 1999-117370 19990127
US 1998-117370 19990127
WO 1999-US13918 19990621
AB Methods are disclosed for detg. a function of cells, which comprises a suspension of cells flowing along a first fluid channel. The cells have a first detectable property assocd. therewith, and the cells produce a second detectable property upon activation of the function of the cells, the first and second detectable properties being distinguishable from each other. The levels of the first and second detectable properties are measured. The level of second detectable property is compared to the level of first detectable property to det. the relative function of the cells. The methodol. of the invention is useful in e.g. the drug discovery process.
RE.CNT 16
RE
(1) Allelix Biopharmaceuticals Inc; WO 9858074 A2 1998 HCAPLUS
(2) Asgari; US 5629147 A 1997 HCAPLUS
(3) Bresser; US 5225326 A 1993 HCAPLUS
(4) Brunk; Biophysical Journal 1997, V72, P2820 HCAPLUS
(6) Glucksmann; US 5795726 A 1998 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:641026 HCAPLUS
DN 131:267987
TI Cancer diagnosis and therapy based on expression levels of p53-regulated genes
IN Levine, Arnold J.; Murphy, Maureen E.; Mack, David H.; Gish, Kurt C.; Tom, Edward Yat Wah
PA Affymetrix, Inc., USA; Princeton University
SO PCT Int. Appl., 46 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9950456	A1	19991007	WO 1999-US6656	19990326 <--
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6020135	A	20000201	US 1998-49025	19980327 <--
	AU 9932085	A1	19991018	AU 1999-32085	19990326 <--
	EP 1064404	A1	20010103	EP 1999-914184	19990326 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6171798	B1	20010109	US 1999-442039	19991117 <--
PRAI	US 1998-49025	19980327 <--			
	WO 1999-US6656	19990326			

AB Many genes are identified as being p53-regulated which were not heretofore known to be p53-regulated. This includes both genes whose expression is induced and genes whose expression is repressed by the expression of wild-type p53. The effects of p53 expression on gene expression in Eb-1 cells was tested by hybridizing to a chip that contains deoxyoligonucleotide sequences (25-mers) that derived from a database of 6800 known genes or EST sequences. Seventy genes were induced by p53 and 77 were repressed by p53. Monitoring expression of these genes is used to provide indications of p53 status in a cell. Such monitoring can also be used to screen for useful anticancer therapeutics, as well as for substances which are carcinogenic. Defects in p53 can be bypassed by supplying p53 induced genes to cells. Defects in p53 can also be bypassed by supplying antisense constructs to p53-repressed genes.

IT **140108-55-0**, GenBank Z11502
RL: BOC (Biological occurrence); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(gene induced by p53; cancer diagnosis and therapy based on expression levels of p53-regulated genes)

IT **132702-51-3**, GenBank J04543
RL: BOC (Biological occurrence); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(gene repressed by p53; cancer diagnosis and therapy based on expression levels of p53-regulated genes)

RE.CNT 9
RE
(2) Genzyme Corp; WO 9901581 A 1999 HCAPLUS
(3) Madden, S; CANCER RESEARCH 1996, V56(23), P5384 HCAPLUS
(4) Madden, S; ONCOGENE 1997, V15(9), P1079 HCAPLUS
(5) Onyx Pharmaceuticals; WO 9418992 A 1994 HCAPLUS
(6) Polyak, K; NATURE 1997, V389, P300 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:405112 HCAPLUS
DN 131:56155
TI Methods for the simultaneous identification of novel biological targets and lead structures for drug development using combinatorial libraries and probes
IN Heefner, Donald L.; Zepp, Charles M.; Gao, Yun; Jones, Steven W.
PA Sepracor Inc., USA

SO PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9931267	A1	19990624	WO 1998-US26894	19981218 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9919256	A1	19990705	AU 1999-19256	19981218 <--
EP 1049796	A1	20001108	EP 1998-964053	19981218 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1997-68035 19971218 <--
WO 1998-US26894 19981218
AB The combinatorial screening assays and detection methods of the present invention encompass highly diversified libraries of compds. which act as fingerprints to allow for the identification of specific mol. differences existing between biol. samples. The combinatorial screening assay and detection methods of the present invention utilize highly diversified libraries of compds. to interrogate and characterize complex mixts. in order to identify specific mol. differences existing between biol. samples, which may serve as targets for diagnosis of development of therapeutics. The invention is base, in part, on the design of sensitive, rapid, homogeneous assay systems that permit the evaluation, interrogation, and characterization of samples using complex, highly diversified libraries of mol. probes. The ability to run the high throughput assays in a homogeneous format increases sensitivity of screening. In addn., the homogeneous format allows the mols. which interact to maintain their native or active conformations. Moreover, the homogeneous assay systems of the invention utilize robust detection systems that do not require sepn. steps for detection of reaction products. The assays of the invention can be used for diagnostics, drug screening and discovery, target-driven discover, and in the field of proteomics and genomics for the identification of disease markers and drug targets.
RE.CNT 1
RE
(1) Lin; Science 1997, V278, P840 HCAPLUS

L108 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:325806 HCAPLUS
DN 130:349392
TI Diagnostic and medicinal use of host-derived proteins binding hepatitis C virus
IN Maertens, Geert; Depla, Erik
PA Innogenetics N.V., Belg.
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9924054	A1	19990520	WO 1998-EP7107	19981106 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,				

UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9915610 A1 19990531 AU 1999-15610 19981106 <--
EP 1028742 A1 20000823 EP 1998-959859 19981106 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRAI EP 1997-870178 19971106 <--
WO 1998-EP7107 19981106
AB The finding that the human proteins **annexin** V, tubulin and apolipoprotein B bind to the hepatitis C virus envelope proteins E1 and/or E2 and the usage of these human proteins to diagnose and treat an infection with hepatitis C virus are described. The usage of the latter proteins to enrich HCV envelope proteins and mols. which inhibit binding of HCV to these human proteins, as well as vaccines employing the E1 and/or E2 binding domains are also disclosed.
RE.CNT 5
RE
(1) Depla, E; Hepatology 1998, V28(4 Part 2), P272A
(2) Innogenetics NV; WO 9604385 A 1996 HCAPLUS
(3) Melki, R; Virology 1994, V202, P339 HCAPLUS
(4) NV Innogenetics SA; WO 9401554 A 1994 HCAPLUS
(5) Thomssen, R; DE 4206574 C 1993 HCAPLUS

L108 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:282074 HCAPLUS
DN 130:316598
TI Targetable lipid vesicle particles for detection and treatment of cells
IN Clarke, David John; Harrison, Michael Henry
PA The Victoria University of Manchester, UK
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920252	A1	19990429	WO 1998-GB3071	19981014 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9895473	A1	19990510	AU 1998-95473	19981014 <--
EP 1023047	A1	20000802	EP 1998-949090	19981014 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

NO 2000001976	A	20000615	NO 2000-1976	20000414 <--

PRAI GB 1997-21901 19971016 <--
WO 1998-GB3071 19981014 <--
AB Lipid vesicle particles are disclosed which are capable of being targeted to a cell type of interest, said particle incorporating a peptide which is responsive to a predetd. metabolic signal from the targeted cell so as to modulate the permeability of the particle, said particle further incorporating a species to be targeted to the cell which is activated on said modulation of permeability. The particles may be used in methods for detecting cells, methods of treating cells and also therapeutically, e.g., in cancer therapy. The method can be applied also to detection and removal of pathogenic cells in a water source.
RE.CNT 7
RE
(1) Bally, M; US 4885172 A 1989 HCAPLUS
(2) Otsuka Pharmaceutical Co, Ltd; EP 0393707 A 1990 HCAPLUS

(3) President and Fellows of Harvard College; WO 9640060 A 1996 HCAPLUS
(4) The Liposome Company, Inc; WO 9816240 A 1998 HCAPLUS
(5) University of Massachusetts Medical Center; WO 9325225 A 1993 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:189230 HCAPLUS
DN 130:191865
TI Assays for detecting modulators of cytoskeletal function
IN Vale, Ron; Pierce, Daniel; Spudich, James; Goldstein, Lawrence S. B.
PA Board of Trustees of Leland Stanford Jr. University, USA; Regents of the University of California
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9911814	A1	19990311	WO 1998-US18368	19980903 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893018	A1	19990322	AU 1998-93018	19980903 <--
EP 1009853	A1	20000621	EP 1998-945872	19980903 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1997-57895 19970904 <--
WO 1998-US18368 19980903 <--
AB Described herein are methods of identifying compds. which modulate the activity of the cytoskeletal system. The methods are rapid, convenient and sensitive. Preferably, the method is used to identify lead compds. that can be used as therapeutics, diagnostics and agricultural agents. Generally, test compds. are added to two cytoskeletal components which bind to one another, to det. whether the binding is affected by the test compd. Wherein the binding is affected, a compd. which modulates the cytoskeletal system is identified.
RE.CNT 5
RE
(1) Endow; J Cell Sci 1996, V109, P2429 HCAPLUS
(2) Gerisch; Curr Biol 1995, V5(11), P1280 HCAPLUS
(3) Ludin; Gene 1996, V173, P107 HCAPLUS
(4) Ma; Proc Soc Natl Acad Sci USA 1996, V93, P12998 HCAPLUS
(5) Olson; J Cell Biol 1995, V130(3), P639 HCAPLUS

L108 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:326292 HCAPLUS
DN 124:337368
TI Method for the determination of the prethrombotic state
IN Freyssinet, Jean-marie; Antoni, Benedicte; Donie, Frederic; Lill, Helmut
PA Boehringer Mannheim Gmbh, Germany
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9603655	A1	19960208	WO 1995-EP2846	19950719 <--
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

```
     EP 772778          A1   19970514       EP 1995-942622   19950719 <--
     EP 772778          B1   19991027
        R:  AT, CH, DE, ES, FR, IT, LI
     JP 10503023        T2   19980317       JP 1995-505441   19950719 <--
     AT 186121          E    19991115       AT 1995-942622   19950719 <--
     ES 2139957         T3   20000216       ES 1995-942622   19950719 <--
PRAI EP 1994-111514    19940723  <--
     WO 1995-EP2846    19950719  <--
```

AB The present invention relates to a method for detg. the prethrombotic state of an individual. More specifically, the present invention relates to a method for the detn. of the circulating microparticles and/or stimulated procoagulant cells, to a method for the detn. of a special category of circulating microparticles and/or stimulated procoagulant cells as well as to a method for the detn. of phospholipid-binding antibodies which are related to diseases with an increased thrombotic risk or to diseases assocd. with apoptosis.

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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 4 April 2001 (20010404/ED)

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for details.

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L121 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:63389 BIOSIS
DN PREV199900063389
TI Increased expression of **annexin** I and thioredoxin detected by two-dimensional gel electrophoresis of drug **resistant** human stomach cancer cells.
AU Sinha, Pranav (1); Huetter, Gero; Koettgen, Eckart; Dietel, Manfred; Schadendorf, Dirk; Lage, Hermann
CS (1) Inst. Laboratoriumsmed. und Pathobiochem., Campus Virchow-Klinikum, Universitaetsklin. Charite, Augustenburger Platz 1, Berlin Germany
SO Journal of Biochemical and Biophysical Methods, (**Nov. 18, 1998**) Vol. 37, No. 3, pp. 105-116.
ISSN: 0165-022X.
DT Article
LA English
AB The therapy of advanced cancer using chemotherapy alone or in combination with radiation or hyperthermia yields an overall response rate of about 20-50%. This success is often marred by the development of **resistance** to cytostatic drugs. Our aim was to study the global analysis of protein expression in the development of **chemoresistance** in vitro. We therefore used a cell culture model derived from the gastric carcinoma cell line EPG 85-257P. A classical **multidrug-resistant** subline EPG85-257RDB selected to daunorubicin and an atypical **multidrug-resistant** cell variant EPG85-257RNOV selected to mitoxantrone, were analysed using two-dimensional electrophoresis in immobilized pH-gradients (pH 4.0-8.0) in the first dimension and linear polyacrylamide gels (12%) in the second dimension. After staining with coomassie brilliant blue, image analysis was performed using the PDQuest system. Spots of interest were isolated using preparative two-dimensional electrophoresis and subjected to microsequencing. A total of 241 spots from the EPG85-257RDB-standard and

bad date

289 spots from the EPG85-257RNOV-standard could be matched to the EPG85-257P-standard. Microsequencing after enzymatic hydrolysis in gel, mass spectrometric data and sequencing of the peptides after their fractionation using microbore HPLC identified that two proteins **annexin** I and thioredoxin were overexpressed in **chemoresistant** cell lines. **Annexin** I was present in both the classical and the atypical **multidrug-resistant** cells. Thioredoxin was found to be overexpressed only in the atypical **multidrug-resistant** cell line.

CC Biochemical Methods - General *10050
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General *10060
Digestive System - General; Methods *14001
Neoplasms and Neoplastic Agents - General *24002
BC Hominidae 86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques; Tumor Biology
IT Diseases
stomach cancer: digestive system disease, in vitro, neoplastic disease
IT Chemicals & Biochemicals
annexin I: expression; coomassie brilliant blue: dye; daunorubicin: antineoplastic - drug; mitoxantrone: antineoplastic - drug; thioredoxin: expression; trichloroacetic acid
IT Alternate Indexing
Stomach Neoplasms (MeSH)
IT Methods & Equipment
cell culture: Cell Culture Techniques, culture method; image analysis: Analysis/Characterization Techniques: CB, analytical method; linear polyacrylamide gel: laboratory equipment; mass spectrometry: analytical method, spectroscopic techniques: CB; microsequencing: sequencing method, sequencing techniques; protein expression analysis: Analysis/Characterization Techniques: CB, analytical method; solubilisation: Rabilloud, cell disruption techniques, cell modification method; turbidimetric assay: Qualitative/Quantitative Techniques, determination method; two-dimensional gel electrophoresis: analytical method, polyacrylamide gel electrophoresis; Dynatech MR 7000 ELISA photometer: Dynatech, laboratory equipment; HPLC [high performance liquid chromatography]: analytical method, liquid chromatography; PDQuest system: laboratory equipment; 96-well microtiter plates: Nunc, laboratory equipment
IT Miscellaneous Descriptors
chemoresistance; immobilized pH-gradients
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
EPG 85-257P cell line (Hominidae): human gastric carcinoma cells; EPG85-257RDB cell line (Hominidae): classical **multidrug-resistant** subline, human gastric carcinoma cells; EPG85-257RNOV cell line (Hominidae): atypical **multi-drug resistant** cell variant, human gastric carcinoma cells
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 20830-81-3 (DAUNORUBICIN)
65271-80-9 (MITOXANTRONE)
9003-05-8 (POLYACRYLAMIDE)
74434-20-1 (COOMASSIE BRILLIANT BLUE)
76-03-9 (TRICHLOROACETIC ACID)

L121 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:53368 BIOSIS
DN PREV199900053368
TI 2-Deoxy-D-glucose preferentially kills **multidrug-resistant** human KB carcinoma cell lines by apoptosis.
AU Bell, S. E.; Quinn, D. M.; Kellett, G. L.; Warr, J. R. (1)
CS (1) Dep. Biology, University York, P.O. Box 373, York YO10 5YW UK

SO British Journal of Cancer, (**Dec., 1998**) Vol. 78, No. 11, pp. 1464-1470.
ISSN: 0007-0920.
DT Article
LA English
AB The aim of this study was to determine the mechanism of cell death associated with the preferential killing of **multidrug-resistant** (**MDR**) cells by the glycolytic inhibitor 2-deoxy-D-glucose (2DG) in a range of **MDR** human KB carcinoma cell lines selected in different drugs. The D10 values for KB-V1, KB-C1 and KB-A1 (selected in vinblastine, colchicine and doxorubicin respectively) were 1.74, 1.04 and 0.31 mm, respectively, compared with 4.60 mm for the parental cell line (KB-3-1). The mechanism of cell death was identified as apoptosis, based on nuclear morphology, **annexin** V binding and poly(ADP-ribose) polymerase (PARP) cleavage. 2DG induced apoptosis in the three **MDR** cell lines in a dose- and time-dependent manner and did not induce necrosis. PARP cleavage was detected in KB-C1 cells within 2 h of exposure to 50 mm 2DG and slightly later in KB-A1 and KB-V1 cells. The relative levels of 2DG sensitivity did not correlate with the levels of **multidrug resistance** or with the reduced levels of the glucose transporter GLUT-1 in these cells. We speculate that a 2DG-stimulated apoptotic pathway in **MDR** KB cells differs from that in normal KB cells.
CC **Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008**
Cytology and Cytochemistry - Human *02508
Integumentary System - Pathology *18506
Pharmacology - Integumentary System, Dental and Oral Biology *22020
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines *24005
Biochemical Studies - General *10060
Biochemical Studies - Carbohydrates *10068
Pathology, General and Miscellaneous - Necrosis *12510
Pathology, General and Miscellaneous - Therapy *12512
Tissue Culture, Apparatus, Methods and Media *32500
BC Hominidae 86215
IT Major Concepts
Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
2-deoxy-D-glucose: antineoplastic - drug
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
KB cell line (Hominidae): drug-induced apoptosis, human epidermoid carcinoma cell line, in-vitro model system, **multidrug resistance**
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 154-17-6 (2-DEOXY-D-GLUCOSE)

L121 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:457904 BIOSIS
DN PREV199800457904
TI Increased expression of **annexin** I and thioredoxin is associated with drug resistance in human gastric cancer.
AU Sinha, Pranav (1); Huetter, Gero; Koettgen, Eckart; Dietel, Manfred; Schadendorf, Dirk; Lage, Hermann
CS (1) Inst. Klin. Chem. Biochem., Charite, Campus Virchow-Klin., Augustenburger Platz 1, 13353 Berlin Germany
SO Journal of Molecular Medicine (Berlin), (**May, 1998**) Vol. 76, No. 6, pp. B47.
Meeting Info.: 2nd Congress of Molecular Medicine Berlin, Germany May 6-9, 1998
ISSN: 0946-2716.
DT Conference
LA English
CC **Neoplasms and Neoplastic Agents - General *24002**

Cytology and Cytochemistry - General *02502
Genetics and Cytogenetics - General *03502
Biochemical Studies - General *10060
Metabolism - General Metabolism; Metabolic Pathways *13002
Digestive System - General; Methods *14001
Pharmacology - General *22002
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
annexin I: expression; daunorubicin: antineoplastic - drug; mitoxantrone: antineoplastic - drug; thioredoxin: expression
IT Methods & Equipment
two-dimensional electrophoresis: analytical method
IT Miscellaneous Descriptors
chemoresistance; Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
EPG85-257P (Hominidae): human gastric carcinoma cells
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 65271-80-9 (MITOXANTRONE)
20830-81-3 (DAUNORUBICIN)

L121 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:217080 BIOSIS
DN PREV199800217080
TI Short course infusional idarubicin plus intermittent cytarabine and etoposide for refractory hematologic malignancies: Clinical and preliminary pharmacological results.
AU Bassan, Renato (1); Chiodini, Barbara; Zucchetti, Massimo; Lerede, Teresa; Cornelli, Pier Emilio; Cortelazzo, Sergio; Barbui, Tiziano
CS (1) Div. Ematologia, Ospedali Riuniti, Largo Barozzi 1, 24100 Bergamo Italy
SO Haematologica, (**Jan.**, **1998**) Vol. 83, No. 1, pp. 27-33.
ISSN: 0390-6078.
DT Article
LA English
AB Background and Objective. Idarubicin (IDA) is relatively immune to the **multidrug resistance** P-gp mechanism that is frequently expressed in recurrent and refractory hematologic malignancies. Owing to rapid metabolism in vivo, a continuous infusion (CI) of IDA might prolong exposure time to the parent drug rather than its more P-gp susceptible alcohol metabolite. For this reason we developed a brief retreatment schedule incorporating CI IDA in order to obtain clinical as well as preliminary pharmacological data in patients with refractory leukemias and lymphomas. Design and Methods. Eligible patients had either advanced-stage acute myeloid or lymphoid leukemias (AML, ALL) or high-grade non-Hodgkin's lymphomas (NHL) which failed curative-intent frontline or salvage regimens in use at our institution during the study period (July-October 1992). CI IDA 5 mg/m2/d was employed together with intermittent (every 8 hours) intermediate-dose cytarabine (500 mg/m2) and etoposide (200 Mg/M2); all drugs were given for 2-4 days. A preliminary pharmacokinetic evaluation of CI IDA was carried out in three patients, including a comparison with bolus delivery in one. The in vitro effects of CI-type vs bolus-type IDA delivery in terms of intracellular IDA accumulation and related pro-apoptotic activity were assessed in P-gp- and P-gp+ human leukemic CEM cells by means of cytofluorimetry (IDA fluorescence Intensity = FI, **annexin** V expression), with and without the addition of P-gp inhibitor cyclosporin A (CsA). Results. Complete (2) or partial (4) responses were achieved in a total of 12 patients (17% and 33%, respectively), despite prior treatments with anthracyclines (100% of

cases) and cytarabine-etoposide (33% of cases). Hematological toxicity caused the duration of treatment to be reduced from 4 days to 2 days after the first 4 patients. The procedural death rate was 42% (5/12), which was probably related in part to the sum of adverse prognostic characteristics: median patient age 55 years, two-thirds of cases having previously failed second/third-line regimens. The pharmacokinetic study showed an increased plasma AUC value with CI IDA in one patient (2.9-fold increase vs bolus delivery) due to the prolonged presence of low IDA plasma levels (10-20 ng/mL vs 50 ng/mL), as seen in two other cases as well. On the other hand, the in vitro study did not prove to be in favor of CI IDA because the R threshold (>1500 units) associated with increased apoptosis of P-gp, cells (>10%) was achieved only with bolus-type IDA exposure (50 ng/mL for 30') plus CsA. Interpretation and conclusions. This short regimen demonstrated activity against end-stage leukemias and lymphomas and might prove to be more effective and less toxic In younger patients and in those with less advanced disease. In view of the results from plasma pharmacokinetics and in vitro intracellular IDA accumulation and apoptosis assays in lymphoblastic CEM cells, CI IDA 5 mg/m2/day may not represent a better therapeutic option than a rapid bolus injection, particularly in P-gp+ neoplasms. If obtaining an adequate intracellular drug concentration is the primary treatment goal, a higher CI IDA dosage, the addition of a P-gp down-regulator such as CsA and others, and an in vivo study focusing on tumor samples from patients could all be helpful.

CC Pharmacology - General *22002
Blood, Blood-Forming Organs and Body Fluids - General; Methods *15001
Neoplasms and Neoplastic Agents - General *24002

BC Hominidae 86215

IT Major Concepts
Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Diseases
acute lymphoid leukemia: blood and lymphatic disease, refractory hematologic malignancy, immune system disease, neoplastic disease; acute myeloid leukemia: blood and lymphatic disease, neoplastic disease, refractory hematologic malignancy; non-Hodgkin's lymphoma: blood and lymphatic disease, refractory hematologic malignancy, immune system disease, neoplastic disease

IT Chemicals & Biochemicals
cytarabine: antineoplastic - drug, intermittent; etoposide: antineoplastic - drug; idarubicin: antineoplastic - drug, infusion, pharmacokinetics, short course

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): patient

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 58957-92-9 (IDARUBICIN)
147-94-4 (CYTARABINE)
33419-42-0 (ETOPOSIDE)

L121 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1992:306370 BIOSIS

DN BA94:19520

TI ELEVATED EXPRESSION OF **ANNEXIN** II LIPOCORTIN II P36 IN A **MULTIDRUG RESISTANT** SMALL CELL LUNG CANCER CELL LINE.

AU COLE S P C; PINKOSKI M J; BHARDWAJ G; DEELEY R G

CS CANCER RES. LAB., ROOM 331 BOTTERELL HALL, QUEEN'S UNIV., KINGSTON, ONTARIO K7L 3N6, CAN.

SO BR J CANCER, (1992) 65 (4), 498-502.
CODEN: BJCAAI. ISSN: 0007-0920.

FS BA; OLD

LA English

AB The doxorubicin-selected **multidrug resistant** small cell lung cancer cell line, H69AR, is cross-**resistant** to the Vinca alkaloids and epipodophyllotoxins, but does not overexpress P-glycoprotein, a 170 kDa plasma membrane efflux pump usually associated

with this type of **resistance**. Monoclonal antibodies were raised against the H69AR cell line and one of these, MAb 3.186, recognises a peptide epitope on a 36 kDa phosphorylated protein that is membrane associated, but not presented on the external surface of H69AR cells (Mirski & Cole, 1991). In the present study, in vitro translation and molecular cloning techniques were used to determine the relative levels of mRNA corresponding to the 3.186 antigen. In addition, a cDNA clone containing an insert of approximately 1.4 was obtained by screening an H69AR cDNA library with 125I-MAb 3.186. Fragments of this cloned DNA hybridised to a single mRNA species of approximately 1.6 kb that was 5 to 6-fold elevated in H69AR cells. Partial DNA sequencing and restriction endonuclease mapping revealed identity of the cloned DNA with p36, a member of the **annexin**/lipocortin family of Ca2+ and phospholipid binding proteins.

CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Carbohydrates 13004
Metabolism - Proteins, Peptides and Amino Acids 13012
Respiratory System - Pathology *16006
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Respiratory System *22030
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008

BC Hominidae 86215

IT Miscellaneous Descriptors
HUMAN DOXORUBICIN ANTINEOPLASTIC-DRUG

RN 23214-92-8 (DOXORUBICIN)

L121 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1992:282892 BIOSIS

DN BA94:7542

TI THE 1991 MERCK FROSST AWARD **MULTIDRUG RESISTANCE** IN SMALL CELL LUNG CANCER.

AU COLE S P C

CS CANCER RES. LAB., QUEEN'S UNIV., KINGSTON, ONT., CANADA K7L 3N6.

SO CAN J PHYSIOL PHARMACOL, (1992) 70 (3), 313-329.
CODEN: CJPPA3. ISSN: 0008-4212.

FS BA; OLD

LA English

AB The two-year survival rate of patients with small cell lung cancer is less than 10%. The major reason for this poor outcome is the development of drug **resistance**. Panels of small cell lung cancer cell lines have been established, providing models for the study of drug **resistance** in this tumour. One such model is the doxorubicin-selected H69AR cell line. H69AR displays the typical **multidrug resistance** phenotype in that it is cross-**resistant** to anthracyclines, Vinca alkaloids (e.g., vinblastine) and epipodophyllotoxins (e.g. VP-16). However, H69AR cells do not overexpress P-glycoprotein, the membrane drug efflux pump frequently found on **multidrug resistant** cells. Some alterations in glutathione levels and associated enzyme activities were found but the data do not support the notion that enhanced drug detoxication is involved in H69AR cell **resistance**. Fewer drug-induced DNA strand breaks, reduced levels of topoisomerase II, and reduced formation of drug-stabilized DNA/topoisomerase II complexes were observed in H69AR cells. These data implicate topoismerase II in the **resistance** phenotype of H69AR cells, but cannot explain H69AR cell **resistance** to the Vinca alkaloids, which do not have topoisomerase II as a target. Monoclonal antibodies against antigens overexpressed on H69AR cells have been derived and four have been characterized. Immunoscreening of an H69AR cDNA expression library was allowed the identification of one of these

antigens as p36 (**annexin** II), a Ca2+/phospholipid binding protein. Chemosensitizers and novel xenobiotics have been examined for their ability to circumvent the drug **resistance** of H69AR cells. The limited success of these investigations suggests that innovative approaches may be required. In conclusion, the data obtained with H69AR and other models of small cell lung cancer indicate that multiple mechanisms contribute to drug **resistance** in this disease.

CC Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Respiratory System - Pathology *16006
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008

BC Hominidae 86215

IT Miscellaneous Descriptors
REVIEW HUMAN H69AR CELLS VINBLASTINE VP-16 DNA GLUTATHIONE GLYCOPROTEIN TOPOISOMERASE II MEMBRANE DRUG EFFLUX PUMP ENHANCED DRUG DETOXIFICATION

RN 70-18-8 (GLUTATHIONE)
865-21-4 (VINBLASTINE)
33419-42-0 (VP-16)
80449-01-0 (TOPOISOMERASE)

=> fil cancer medline

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FILE 'MEDLINE' ENTERED AT 09:23:12 ON 11 APR 2001

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L166 ANSWER 1 OF 18 CANCERLIT DUPLICATE 1
AN 1998426076 CANCERLIT
DN 98426076
TI Random versus selective membrane phospholipid oxidation in apoptosis: role of phosphatidylserine.
AU Fabisiak J P; Tyurina Y Y; Tyurin V A; Lazo J S; Kagan V E
CS Department of Environmental and Occupational Health, School of Public Health, University of Pittsburgh, Pennsylvania 15238, USA.
NC ES-09387 (NIEHS)
CA-61299 (NCI)
F05NS10669 (NINDS)
SO BIOCHEMISTRY, **(1998)**. Vol. 37, No. 39, pp. 13781-90.
Journal code: AOG. ISSN: 0006-2960.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 98426076
EM 199812
AB The formation of reactive oxygen species has been associated with apoptosis. To assess the role of lipid peroxidation in apoptosis, we used 2,2'-azobis(2,4-dimethylisovaleronitrile) (AMVN) to generate peroxyl radicals within cellular membranes of HL-60 cells. cis-Parinaric acid (cis-PnA) metabolically integrated into phospholipids of HL-60 cells was used as a probe to assess the extent of lipid peroxidation within specific

phospholipid classes. Within 2 h, AMVN (500 microM) randomly oxidized more than 85% of cis-PnA contained in all major classes of phospholipids. AMVN-induced lipid peroxidation was followed by apoptosis as determined by nuclear condensation, DNA fragmentation, and **annexin** V binding to externalized phosphatidylserine (PS). Fluorescamine derivatization of external aminophospholipids revealed that PS, but not phosphatidylethanolamine, was externalized. The vitamin E analogue, 6-hydroxy-2,2,5,7,8-pentamethylchromane (PMC), inhibited overall oxidation of cis-PnA in phospholipids by more than 85%. Not all phospholipids, however, were equally protected. Phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and sphingomyelin were nearly completely protected by PMC, while oxidation of PS was unaffected in whole living cells. The insensitivity of PS to PMC was not an intrinsic property because PMC protected all lipids equally during AMVN oxidation of liposomes prepared from cis-PnA-labeled cells. The potential role for PS oxidation in apoptosis was further suggested by the faithful execution of apoptosis following coexposure of cells to AMVN and PMC.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antioxidants: PD, pharmacology
*Apoptosis
Apoptosis: DE, drug effects
Azo Compounds: PD, pharmacology
Chromans: PD, pharmacology
Drug Resistance
Fatty Acids, Unsaturated: ME, metabolism
HL-60 Cells
Lipid Peroxidation: DE, drug effects
*Membrane Lipids: ME, metabolism
Nitriles: PD, pharmacology
Oxidation-Reduction: DE, drug effects
Phosphatidylserines: ME, metabolism
*Phosphatidylserines: PH, physiology
*Phospholipids: ME, metabolism

RN 18427-44-6 (parinaric acid); 4419-11-8 (2,2'-azobis(2,4-dimethylvaleronitrile)); 950-99-2 (2,2,5,7,8-pentamethyl-1-hydroxychroman)

CN 0 (Antioxidants); 0 (Azo Compounds); 0 (Chromans); 0 (Fatty Acids, Unsaturated); 0 (Membrane Lipids); 0 (Nitriles); 0 (Phosphatidylserines); 0 (Phospholipids)

L166 ANSWER 2 OF 18 CANCERLIT DUPLICATE 2

AN 1998227981 CANCERLIT

DN 98227981

TI Overexpression of Bax gene sensitizes K562 erythroleukemia cells to apoptosis induced by selective chemotherapeutic agents.

AU Kobayashi T; Ruan S; Clodi K; Kliche K O; Shiku H; Andreeff M; Zhang W

CS Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.

NC CA55164 (NCI)
CA57639 (NCI)
CA16672 (NCI)

SO ONCOGENE, **(1998)**. Vol. 16, No. 12, pp. 1587-91.
Journal code: ONC. ISSN: 0950-9232.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; L; Priority Journals; Cancer Journals

LA English

OS MEDLINE 98227981

EM 199806

AB Bax and Bcl-2 are a pair of important genes that control programmed cell death, or apoptosis, with Bax being the apoptosis promoter and Bcl-2 the apoptosis protector. Although the detailed mechanism is unknown, the protein products of these two genes form protein dimers with each other and the relative ratio of the two proteins is believed to be a determinant of the balance between life and death. In our preliminary study, we found that K562 erythroleukemia cells have an extremely low level of endogenous Bcl-2 expression and a fairly high level of endogenous Bax expression. We constructed Bax and Bcl-2 expression vectors and transfected them into

K562 cells. We found that transfection of Bax vector increased the expression of Bax protein; a shortened form of Bax also appeared. Cell death analysis using the **Annexin** V assay showed that the Bax vector caused significantly more apoptotic cells that the Bcl-2 or pCI-neo vector did. After selection with G418, Bax, Bcl-2 and pCI-neo stably transfected cells were established. These three cell lines were examined for their response to the chemotherapeutic agents ara-C, doxorubicin, etoposide and SN-38. Bax-K562 cells showed significantly higher fractions of apoptotic cells than pCI-neo-K562 cells when treated with ara-C, doxorubicin or SN-38. No sensitization effect was seen when etoposide was used. In contrast, Bcl-2-K562 cells had fewer apoptotic cells than pCI-neo-K562 cells after treatment with all these agents. Therefore, Bax may sensitize K562 cells to apoptosis induced by a wide range of, but not all, chemotherapeutic agents.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Apoptosis: DE, drug effects
*Apoptosis: GE, genetics
Drug Resistance, Neoplasm
*Gene Expression Regulation, Neoplastic: DE, drug effects
***Leukemia, Erythroblastic, Acute: DT, drug therapy**
***Leukemia, Erythroblastic, Acute: GE, genetics**
Leukemia, Erythroblastic, Acute: PA, pathology
Proto-Oncogene Proteins: BI, biosynthesis
*Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis
*Proto-Oncogenes: DE, drug effects
Transfection
Tumor Cells, Cultured

CN 0 (Bax protein); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Proto-Oncogene Proteins)

L166 ANSWER 3 OF 18 CANCERLIT DUPLICATE 3
AN 1999052297 CANCERLIT
DN 99052297
TI 2-Deoxy-D-glucose preferentially kills **multidrug-resistant** human KB carcinoma cell lines by apoptosis.
AU Bell S E; Quinn D M; Kellett G L; Warr J R
CS Department of Biology, The University of York, UK.
SO BRITISH JOURNAL OF CANCER, **(1998)**. Vol. 78, No. 11, pp. 1464-70.
Journal code: AV4. ISSN: 0007-0920.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 99052297
EM 199901
AB The aim of this study was to determine the mechanism of cell death associated with the preferential killing of **multidrug-resistant** (**MDR**) cells by the glycolytic inhibitor 2-deoxy-D-glucose (2DG) in a range of **MDR** human KB carcinoma cell lines selected in different drugs. The D10 values for KB-V1, KB-C1 and KB-A1 (selected in vinblastine, colchicine and doxorubicin respectively) were 1.74, 1.04 and 0.31 mM, respectively, compared with 4.60 mM for the parental cell line (KB-3-1). The mechanism of cell death was identified as apoptosis, based on nuclear morphology, **annexin** V binding and poly(ADP-ribose) polymerase (PARP) cleavage. 2DG induced apoptosis in the three **MDR** cell lines in a dose- and time-dependent manner and did not induce necrosis. PARP cleavage was detected in KB-C1 cells within 2 h of exposure to 50 mM 2DG and slightly later in KB-A1 and KB-V1 cells. The relative levels of 2DG sensitivity did not correlate with the levels of **multidrug resistance** or with the reduced levels of the glucose transporter GLUT-1 in these cells. We speculate that a 2DG-stimulated apoptotic pathway in **MDR** KB cells differs from that in normal KB cells.
CT Check Tags: Human; Support, Non-U.S. Gov't
*Antimetabolites: PD, pharmacology
*Apoptosis

Cell Survival: DE, drug effects
*Deoxyglucose: PD, pharmacology
Dose-Response Relationship, Drug
***Drug Resistance, Multiple**
Drug Resistance, Neoplasm
Flow Cytometry
Microscopy, Fluorescence
Monosaccharide Transport Proteins: ME, metabolism
NAD+ ADP-Ribosyltransferase: ME, metabolism
Time Factors
Tumor Cells, Cultured: DE, drug effects
Tumor Cells, Cultured: ME, metabolism
RN 154-17-6 (Deoxyglucose)
CN EC 2.4.2.30 (NAD+ ADP-Ribosyltransferase); 0 (Antimetabolites); 0 (GLUT-1 protein); 0 (Monosaccharide Transport Proteins)

L166 ANSWER 4 OF 18 CANCERLIT DUPLICATE 4
AN 1998345323 CANCERLIT
DN 98345323
TI Use of the microculture kinetic assay of apoptosis to determine chemosensitivities of leukemias.
AU Kravtsov V D; Greer J P; Whitlock J A; Koury M J
CS Department of Medicine, the Division of Hematology and the Department of Pediatrics, the Division of Pediatric Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA.
SO BLOOD, **(1998)**. Vol. 92, No. 3, pp. 968-80.
Journal code: A8G. ISSN: 0006-4971.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Abridged Index Medicus Journals; Priority Journals; Cancer Journals
LA English
OS MEDLINE 98345323
EM 199809
AB Chemotherapeutic agents exert their antitumor effects by inducing apoptosis. The microculture kinetic (MiCK) assay provides an automated, continuous means of monitoring apoptosis in a cell population. We used the MiCK assay to determine the chemosensitivities of the human promyelocytic HL-60 and lymphoblastic CEM cell lines and leukemia cells freshly isolated from patients with acute nonlymphocytic (ANLL) or acute lymphocytic (ALL) leukemias. Continuous monitoring of apoptosis in the MiCK assay permits determination of the time to the maximum apoptosis (Tm) and its two components which are initiation time (Ti) and development time (Td). Duration of the three timing components of apoptosis varies from hours to days depending on the drug, drug concentration, and type of target cells. In the MiCK assay, the extent of apoptosis is reported in kinetic units of apoptosis. Kinetic units are determined by the slope of the curve created when optical density caused by cell blebbing is plotted as a function of time. Using the leukemia cell lines, we define the relationship between kinetic units determined by the MiCK assay and the percentage of morphologically apoptotic cells in the culture. Flow cytometry analysis of apoptosis in **Annexin**-V-fluorescein isothiocyanate-labeled preparations of HL-60 and CEM cells was also used to compare with data obtained by the MiCK assay. The feasibility of the MiCK assay of apoptosis as a chemosensitivity test was confirmed by its comparison with a 3H-thymidine incorporation assay. We show that samples from 10 ANLL and ALL patients patients tested for sensitivity to various doses of idarubicin (IDR), daunorubicin (DNR), or mitoxantrone (MTA) gave the same percentages of apoptotic cells when calculated by the MiCK assay as when determined by morphological analysis. The MiCK assay was used for dose-response analyses of the sensitivities to IDR, DNR, and MTA of leukemia cells from 4 other patients (2 ANLL and 2 ALL). The results from both cell lines and patient samples indicate that ANLL cells are more sensitive than ALL cells to all three of these chemotherapeutic agents. However, for individual patients the chemosensitivities varied significantly among the three chemotherapeutic agents. These varying responses to IDR, DNR, and MTA indicate that the MiCK assay results can be

of potential use in designing a treatment regimen for a specific patient with acute leukemia. Among several drugs of presumed similar efficacy, the MiCK assay can permit the selection of the specific chemotherapeutic agent that causes the most apoptosis in the patient's leukemic cells. Copyright 1998 by The American Society of Hematology.

CT Check Tags: Comparative Study; Female; Human; Male; Support, Non-U.S. Gov't
Acute Disease
Adolescence
Adult
Aged
Annexin V: ME, metabolism
Antineoplastic Agents: CL, classification
*Antineoplastic Agents: PD, pharmacology
*Apoptosis: DE, drug effects
Bone Marrow: PA, pathology
*Cell Culture: MT, methods
Child
Child, Preschool
***Drug Resistance, Neoplasm**
*Drug Screening Assays, Antitumor: MT, methods
Flow Cytometry
HL-60 Cells: DE, drug effects
Kinetics
Leukemia: BL, blood
***Leukemia: DT, drug therapy**
Leukemia: PA, pathology
Leukemia, Lymphocytic, Acute: BL, blood
Leukemia, Lymphocytic, Acute: DT, drug therapy
Leukemia, Lymphocytic, Acute: PA, pathology
Leukemia, Nonlymphocytic, Acute: BL, blood
Leukemia, Nonlymphocytic, Acute: DT, drug therapy
Leukemia, Nonlymphocytic, Acute: PA, pathology
Leukemia, T-Cell, Acute: PA, pathology
Middle Age
Nephelometry and Turbidimetry
Sensitivity and Specificity
*Tumor Stem Cells: DE, drug effects

CN **0 (Annexin V)**; 0 (Antineoplastic Agents)

L166 ANSWER 5 OF 18 CANCERLIT DUPLICATE 5
AN 1999218599 CANCERLIT
DN 99218599
TI Alteration in p53 pathway and defect in apoptosis contribute independently to cisplatin-resistance.
AU Segal-Bendirdjian E; Mannone L; Jacquemin-Sablon A
CS Unite de Physicochimie et Pharmacologie des Macromolecules Biologiques (CNRS, URA 147), Institut Gustave-Roussy, rue Camille Desmoulins, 94805 Villejuif Cedex, France.
SO CELL DEATH AND DIFFERENTIATION, **(1998)**. Vol. 5, No. 5, pp. 390-400.
Journal code: C7U. ISSN: 1350-9047.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 99218599
EM 199906
AB The accumulation of molecular genetic defects selected during the adaptation process in the development of cisplatin-resistance was studied using progressive cisplatin-resistant variants (L1210/DDP2, L1210/DDP5, L1210/DDP10) derived from a murine leukemia cell line (L1210/0). Of these cell lines, only the most resistant L1210/DDP10 was cross-resistant to etoposide and deficient in apoptosis induced by these two drugs, indicating that resistance to DNA-damaging agents correlates with a defect in apoptosis. This defect was tightly associated with the loss of a Ca2+/Mg2+-dependent nuclear endonuclease activity present in the less

cisplatin-resistant cells. Evidence is presented that p53-dependent function (a) is lost not only in the apoptosis defective L1210/DDP10 cells, but also in the apoptosis susceptible L1210/DDP5 cells; (b) is unrelated to drug-induced cell cycle perturbations. These results suggest that deficiency in the p53 pathway and resistance to DNA-damaging agents due to a defect in apoptosis are independent events.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Annexin V
*Apoptosis: DE, drug effects
Cell Cycle: DE, drug effects
*Cisplatin: PD, pharmacology
Cyclin B: ME, metabolism
Cyclins: ME, metabolism
***Drug Resistance: GE, genetics**
DNA Fragmentation: DE, drug effects
Endonucleases: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
Etoposide: PD, pharmacology
Fluorescein-5-isothiocyanate
Gene Expression Regulation, Neoplastic
Mice
Nuclear Proteins: ME, metabolism
*Protein p53: GE, genetics
Staurosporine: PD, pharmacology
Tumor Cells, Cultured

RN 15663-27-1 (Cisplatin); 3326-32-7 (Fluorescein-5-isothiocyanate); 33419-42-0 (Etoposide); 62996-74-1 (Staurosporine)

CN EC 3.1.- (Endonucleases); 0 (cyclin B1); **0 (Annexin V)**; 0 (Cip1 protein); 0 (Cyclin B); 0 (Cyclins); 0 (Enzyme Inhibitors); 0 (Nuclear Proteins); 0 (Protein p53)

L166 ANSWER 6 OF 18 CANCERLIT DUPLICATE 6

AN 1998176683 CANCERLIT

DN 98176683

TI Elevated Bcl-2/Bax are a consistent feature of apoptosis resistance in B-cell chronic lymphocytic leukaemia and are correlated with in vivo chemoresistance.

AU Pepper C; Hoy T; Bentley P

CS Department of Haematology, Llandough Hospital, Penarth, South Glamorgan, UK.

SO LEUKEMIA AND LYMPHOMA, **(1998)**. Vol. 28, No. 3-4, pp. 355-61. Journal code: BNQ. ISSN: 1042-8194.

DT Journal; Article; (JOURNAL ARTICLE)

FS MEDL; L; Priority Journals

LA English

OS MEDLINE 98176683

EM 199806

AB We investigated the relationship between drug resistance and Bcl-2/Bax in B-cell chronic lymphocytic leukaemia (B-CLL). Apoptosis was induced in vitro with chlorambucil and cell death was monitored by dual-labelled FACS analysis using **Annexin** V and propidium iodide. Bcl-2 and Bax protein expression was quantified using FACS and a correlation between drug-induced apoptosis and Bcl-2/Bax was established. Cells were then sorted into viable and nonviable populations according to their forward and side-scatter characteristics and re-analysed for Bcl-2/Bax. The most resistant cells had elevated Bcl-2 levels and low Bax expression. Furthermore, those cells which were undergoing apoptosis showed only a marginal reduction in Bcl-2 expression, but significantly elevated Bax expression following exposure to chlorambucil. The Bcl-2/Bax was significantly greater in the cell fractions resistant to chlorambucil-induced apoptosis. This observation further supports the suggestion that Bax is the pivotal protein in determining the fate of cells following apoptotic signals.

CT Check Tags: Comparative Study; Human; In Vitro; Support, Non-U.S. Gov't
Antineoplastic Agents, Alkylating: PD, pharmacology
*Apoptosis

Apoptosis: DE, drug effects
Cell Separation
Chlorambucil: PD, pharmacology
Down-Regulation (Physiology)
Drug Resistance, Neoplasm
Flow Cytometry
***Leukemia, B-Cell, Chronic: ME, metabolism**
Leukemia, B-Cell, Chronic: PA, pathology
*Proto-Oncogene Proteins: ME, metabolism
*Proto-Oncogene Proteins c-bcl-2: ME, metabolism
RN 305-03-3 (Chlorambucil)
CN 0 (Antineoplastic Agents, Alkylating); 0 (Bax protein); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Proto-Oncogene Proteins)

L166 ANSWER 7 OF 18 CANCERLIT DUPLICATE 7
AN 1999018867 CANCERLIT
DN 99018867
TI Dexamethasone-induced cytotoxic activity and drug resistance effects in androgen-independent prostate tumor PC-3 cells are mediated by lipocortin 1.
AU Carollo M; Parente L; D'Alessandro N
CS Institute of Pharmacology, Faculty of Medicine, University of Palermo, Italy.
SO ONCOLOGY RESEARCH, **(1998)**. Vol. 10, No. 5, pp. 245-54.
Journal code: BBN. ISSN: 0965-0407.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 99018867
EM 199902
AB We have examined the effects that dexamethasone (DEX), alone or in combination with doxorubicin (DOX), cisplatin (CDDP), or etoposide (VP-16), exerts on the growth of the androgen-independent prostate cancer PC-3 cells. DEX exhibited only a limited cytotoxicity (growth inhibition of about 28% or 20% after 24 or 72 h of exposure, respectively, in the range of DEX 10-100 nM) and did not induce apoptosis in the cells. This cytotoxicity of DEX was mimicked by an active peptide (peptide Ac2-26) drawn from the human lipocortin 1 N-terminus region and abrogated by an antibody to human lipocortin 1. Two inhibitors of arachidonic acid metabolism, tenidap and indomethacin, also caused cytotoxicity. The cytotoxic effects of DEX in combination with DOX, CDDP, or VP-16 were antagonistic when the steroid was administered 3 h before or simultaneously with the drugs. Other schedule-dependency experiments further clarified that, at least in the case of the combination with DOX, it is the steroid that desensitizes the cells to the drug. When peptide Ac2-26, tenidap, or indomethacin were tested in combination with DOX, antagonism was also observed. DEX treatment neither modified the ability of the cells to accumulate DOX nor changed their weak expression of P-glycoprotein. PC-3 cells also produce IL-6, which autocrinally stimulates their growth, and whose gene expression may be reduced by glucocorticoids. In the present experiments DEX only slightly decreased the production and secretion of IL-6 by the cells. The present findings suggest that the slight cytotoxic activity and the drug resistance effects of DEX on PC-3 cells are mediated by induction of lipocortin 1 and inhibition of arachidonic acid metabolism, with no relationship to downregulation of IL-6 levels. These findings indicate also that the combination of DEX with conventional chemotherapeutic agents may result in antagonistic antitumor effects.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Androgens: PD, pharmacology
***Annexin I: PH, physiology**
Apoptosis: DE, drug effects
Arachidonic Acid: ME, metabolism
*Dexamethasone: PD, pharmacology
Doxorubicin: PD, pharmacology
Drug Resistance, Neoplasm

Interleukin-6: SE, secretion
Neoplasms, Hormone-Dependent: DT, drug therapy
P-Glycoprotein: AN, analysis
***Prostatic Neoplasms: DT, drug therapy**
RN 23214-92-8 (Doxorubicin); 50-02-2 (Dexamethasone); 506-32-1 (Arachidonic Acid)
CN 0 (Androgens); **0 (Annexin I)**; 0 (Interleukin-6); 0 (P-Glycoprotein)

L166 ANSWER 8 OF 18 CANCERLIT DUPLICATE 8
AN 1999087009 CANCERLIT
DN 99087009
TI Increased expression of **annexin** I and thioredoxin detected by two-dimensional gel electrophoresis of drug resistant human stomach cancer cells.
AU Sinha P; Hutter G; Kottgen E; Dietel M; Schadendorf D; Lage H
CS Institut fur Laboratoriumsmedizin und Pathobiochemie, Universitatsklinikum Charite, Berlin, Germany.
SO JOURNAL OF BIOCHEMICAL AND BIOPHYSICAL METHODS, **(1998)**. Vol. 37, No. 3, pp. 105-16.
Journal code: H94. ISSN: 0165-022X.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals
LA English
OS MEDLINE 99087009
EM 199903
AB The therapy of advanced cancer using chemotherapy alone or in combination with radiation or hyperthermia yields an overall response rate of about 20-50%. This success is often marred by the development of **resistance** to cytostatic drugs. Our aim was to study the global analysis of protein expression in the development of chemoresistance in vitro. We therefore used a cell culture model derived from the gastric carcinoma cell line EPG 85-257P. A classical **multidrug-resistant** subline EPG85-257RDB selected to daunorubicin and an atypical **multidrug-resistant** cell variant EPG85-257RNOV selected to mitoxantrone, were analysed using two-dimensional electrophoresis in immobilized pH-gradients (pH 4.0-8.0) in the first dimension and linear polyacrylamide gels (12%) in the second dimension. After staining with coomassie brilliant blue, image analysis was performed using the PDQuest system. Spots of interest were isolated using preparative two-dimensional electrophoresis and subjected to microsequencing. A total of 241 spots from the EPG85-257RDB-standard and 289 spots from the EPG85-257RNOV-standard could be matched to the EPG85-257P-standard. Microsequencing after enzymatic hydrolysis in gel, mass spectrometric data and sequencing of the peptides after their fractionation using microbore HPLC identified that two proteins **annexin** I and thioredoxin were overexpressed in chemoresistant cell lines. **Annexin** I was present in both the classical and the atypical **multidrug-resistant** cells. Thioredoxin was found to be overexpressed only in the atypical **multidrug-resistant** cell line.
CT Check Tags: Human; Support, Non-U.S. Gov't
Annexin I: AN, analysis
***Annexin I: ME, metabolism**
Antibiotics, Anthracycline
Antineoplastic Agents: PD, pharmacology
Daunorubicin: PD, pharmacology
***Drug Resistance, Multiple**
Drug Resistance, Multiple: PH, physiology
*Electrophoresis, Gel, Two-Dimensional: MT, methods
Image Processing, Computer-Assisted
Mitoxantrone: PD, pharmacology
Sequence Analysis, DNA
Stomach Neoplasms: DT, drug therapy
***Stomach Neoplasms: ME, metabolism**
Thioredoxin: AN, analysis

*Thioredoxin: ME, metabolism
Tumor Cells, Cultured
RN 20830-81-3 (Daunorubicin); 52500-60-4 (Thioredoxin); 65271-80-9 (Mitoxantrone)
CN **0 (Annexin I)**; 0 (Antibiotics, Anthracycline); 0 (Antineoplastic Agents)

L166 ANSWER 9 OF 18 CANCERLIT DUPLICATE 9
AN 1998203443 CANCERLIT
DN 98203443
TI Short course infusional idarubicin plus intermittent cytarabine and etoposide for refractory hematologic malignancies: clinical and preliminary pharmacological results.
AU Bassan R; Chiodini B; Zucchetti M; Lerede T; Cornelli P E; Cortelazzo S; Barbui T
CS Divisione di Ematologia, Ospedali Riuniti, Bergamo, Italy.
SO HAEMATOLOGICA, **(1998)**. Vol. 83, No. 1, pp. 27-33.
Journal code: FYB. ISSN: 0390-6078.
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L
LA English
OS MEDLINE 98203443
EM 199806
AB BACKGROUND AND OBJECTIVE: Idarubicin (IDA) is relatively immune to the **multidrug resistance** P-gp mechanism that is frequently expressed in recurrent and refractory hematologic malignancies. Owing to rapid metabolism in vivo, a continuous infusion (CI) of IDA might prolong exposure time to the parent drug rather than its more P-gp susceptible alcohol metabolite. For this reason we developed a brief retreatment schedule incorporating CI IDA in order to obtain clinical as well as preliminary pharmacological data in patients with refractory leukemias and lymphomas. DESIGN AND METHODS: Eligible patients had either advanced-stage acute myeloid or lymphoid leukemias (AML, ALL) or high-grade non-Hodgkin's lymphomas (NHL) which failed curative-intent frontline or salvage regimens in use at our institution during the study period (July-October 1992). CI IDA 5 mg/m2/d was employed together with intermittent (every 8 hours) intermediate-dose cytarabine (500 mg/m2) and etoposide (200 mg/m2); all drugs were given for 2-4 days. A preliminary pharmacokinetic evaluation of CI IDA was carried out in three patients, including a comparison with bolus delivery in one. The in vitro effects of CI-type vs bolus-type IDA delivery in terms of intracellular IDA accumulation and related pro-apoptotic activity were assessed in P-gp- and P-gp+ human leukemic CEM cells by means of cytofluorimetry (IDA fluorescence intensity = FI, **annexin** V expression), with and without the addition of P-gp inhibitor cyclosporin A (CsA). RESULTS: Complete (2) or partial (4) responses were achieved in a total of 12 patients (17% and 33%, respectively), despite prior treatments with anthracyclines (100% of cases) and cytarabine-etoposide (33% of cases). Hematological toxicity caused the duration of treatment to be reduced from 4 days to 2 days after the first 4 patients. The procedural death rate was 42% (5/12), which was probably related in part to the sum of adverse prognostic characteristics: median patient age 55 years, two-thirds of cases having previously failed second/third-line regimens. The pharmacokinetic study showed an increased plasma AUC value with CI IDA in one patient (2.9-fold increase vs bolus delivery) due to the prolonged presence of low IDA plasma levels (10-20 ng/mL vs 50 ng/mL), as seen in two other cases as well. On the other hand, the in vitro study did not prove to be in favor of CI IDA because the FI threshold (> 1500 units) associated with increased apoptosis of P-gp+ cells (> 10%) was achieved only with bolus-type IDA exposure (50 ng/mL for 30') plus CsA. INTERPRETATION AND CONCLUSIONS: This short regimen demonstrated activity against end-stage leukemias and lymphomas and might prove to be more effective and less toxic in younger patients and in those with less advanced disease. In view of the results from plasma pharmacokinetics and in vitro intracellular IDA accumulation and apoptosis assays in lymphoblastic CEM cells, CI IDA 5 mg/m2/day may not represent a

better therapeutic option than a rapid bolus injection, particularly in P-gp+ neoplasms. If obtaining an adequate intracellular drug concentration is the primary treatment goal, a higher CI IDA dosage, the addition of a P-gp down-regulator such as CsA and others, and in vivo study focusing on tumor samples from patients could all be helpful.

CT Check Tags: Female; Human; Male
Aged
Antineoplastic Agents, Combined: AD, administration & dosage
*Antineoplastic Agents, Combined: TU, therapeutic use
Child, Preschool
Cytarabine: AD, administration & dosage
*Cytarabine: TU, therapeutic use
Drug Administration Schedule
Drug Resistance, Neoplasm
Etoposide: AD, administration & dosage
*Etoposide: TU, therapeutic use
***Hematologic Neoplasms: DT, drug therapy**
Idarubicin: AD, administration & dosage
*Idarubicin: TU, therapeutic use
*Lymphoproliferative Disorders: DT, drug therapy
Middle Age

RN 147-94-4 (Cytarabine); 33419-42-0 (Etoposide); 58957-92-9 (Idarubicin)
CN 0 (Antineoplastic Agents, Combined)

L166 ANSWER 10 OF 18 CANCERLIT DUPLICATE 10
AN 97466815 CANCERLIT
DN 97466815
TI Bcl-2/Bax ratios in chronic lymphocytic leukaemia and their correlation with in vitro apoptosis and clinical resistance [see comments].
CM Comment in: Br J Cancer 1998 Aug;78(4):553-4
AU Pepper C; Hoy T; Bentley D P
CS Department of Haematology, Llandough Hospital, Penarth, South Glamorgan, UK.
SO BRITISH JOURNAL OF CANCER, **(1997)**. Vol. 76, No. 7, pp. 935-8.
Journal code: AV4. ISSN: 0007-0920.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Cancer Journals; Priority Journals
LA English
OS MEDLINE 97466815
EM 199711
AB The bcl-2 gene is overexpressed in the absence of gene rearrangements in most cases of B-cell chronic lymphocytic leukaemia (B-CLL) and the proto-oncogene product Bcl-2 has been shown to be a regulator of apoptosis. The activity of this protein is opposed by Bax, a homologous protein that accelerates the rate of cell death. B-lymphocyte Bcl-2 and Bax protein levels were found to be significantly altered in B-CLL and increased Bcl-2/Bax ratios were observed in both the treated and untreated patients compared with those of normal controls. These alterations were particularly pronounced in those treated patients found to be clinically unresponsive to chemotherapy. In order to determine whether Bcl-2/Bax ratios affected cell survival via an anti-apoptotic mechanism, cell death was induced in B-CLL cells in vitro using chlorambucil, and apoptosis was monitored by **Annexin** V and propidium iodide staining.
Confirmation that the labelled cells were apoptotic was achieved by morphological assessment of cytospin preparations of cell-sorted populations. Drug-induced apoptosis in B-CLL cells was inversely related to Bcl-2/Bax ratios.

CT Check Tags: Human; Support, Non-U.S. Gov't
*Apoptosis
Drug Resistance, Neoplasm
Flow Cytometry
*Genes, bcl-2: GE, genetics
***Leukemia, B-Cell: ME, metabolism**
Leukemia, B-Cell: PA, pathology
*Neoplasm Proteins: ME, metabolism
*Proto-Oncogene Proteins: ME, metabolism

*Proto-Oncogene Proteins c-bcl-2: ME, metabolism
CN 0 (Bax protein); 0 (Neoplasm Proteins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Proto-Oncogene Proteins)

L166 ANSWER 11 OF 18 CANCERLIT DUPLICATE 11
AN 92222841 CANCERLIT
DN 92222841
TI Elevated expression of **annexin** II (lipocortin II, p36) in a **multidrug resistant** small cell lung cancer cell line.
AU Cole S P; Pinkoski M J; Bhardwaj G; Deeley R G
CS Cancer Research Laboratories, Queen's University, Kingston, Ontario, Canada.
SO BRITISH JOURNAL OF CANCER, **(1992)**. Vol. 65, No. 4, pp. 498-502.
Journal code: AV4. ISSN: 0007-0920.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 92222841
EM 199206
AB The doxorubicin-selected **multidrug resistant** small cell lung cancer cell line, H69AR, is cross-**resistant** to the Vinca alkaloids and epipodophyllotoxins, but does not overexpress P-glycoprotein, a 170 kDa plasma membrane efflux pump usually associated with this type of **resistance**. Monoclonal antibodies were raised against the H69AR cell line and one of these, MAb 3.186, recognises a peptide epitope on a 36 kDa phosphorylated protein that is membrane associated, but not presented on the external surface of H69AR cells (Mirski & Cole, 1991). In the present study, in vitro translation and molecular cloning techniques were used to determine the relative levels of mRNA corresponding to the 3.186 antigen. In addition, a cDNA clone containing an insert of approximately 1.4 kb was obtained by screening an H69AR cDNA library with 125I-MAb 3.186. Fragments of this cloned DNA hybridised to a single mRNA species of approximately 1.6 kb that was 5 to 6-fold elevated in H69AR cells. Partial DNA sequencing and restriction endonuclease mapping revealed identity of the cloned DNA with p36, a member of the **annexin**/lipocortin family of Ca2+ and phospholipid binding proteins.
CT Check Tags: Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal
*Calcium-Binding Proteins: ME, metabolism
***Carcinoma, Small Cell: ME, metabolism**
***Drug Resistance**
DNA: GE, genetics
Gene Expression
***Lung Neoplasms: ME, metabolism**
Precipitin Tests
Restriction Mapping
RNA, Messenger: GE, genetics
Tumor Cells, Cultured
RN 9007-49-2 (DNA)
CN **0 (Annexins)**; 0 (Antibodies, Monoclonal); 0 (Calcium-Binding Proteins); 0 (RNA, Messenger)

L166 ANSWER 12 OF 18 CANCERLIT DUPLICATE 12
AN 92288784 CANCERLIT
DN 92288784
TI The 1991 Merck Frosst Award. **Multidrug resistance** in small cell lung cancer.
AU Cole S P
CS Cancer Research Laboratories, Queen's University, Kingston, Ont., Canada.
SO CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, **(1992)**. Vol. 70, No. 3, pp. 313-29.
Journal code: CJM. ISSN: 0008-4212.
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

FS MEDL; L; Priority Journals
LA English
OS MEDLINE 92288784
EM 199208
AB The two-year survival rate of patients with small cell lung cancer is less than 10%. The major reason for this poor outcome is the development of drug **resistance**. Panels of small cell lung cancer cell lines have been established, providing models for the study of drug **resistance** in this tumour. One such model is the doxorubicin-selected H69AR cell line. H69AR displays the typical **multidrug resistance** phenotype in that it is cross-**resistant** to anthracyclines, Vinca alkaloids (e.g., vinblastine) and epipodophyllotoxins (e.g., VP-16). However, H69AR cells do not overexpress P-glycoprotein, the membrane drug efflux pump frequently found on **multidrug resistant** cells. Some alterations in glutathione levels and associated enzyme activities were found but the data do not support the notion that enhanced drug detoxication is involved in H69AR cell **resistance**. Fewer drug-induced DNA strand breaks, reduced levels of topoisomerase II, and reduced formation of drug-stabilized DNA/topoisomerase II complexes were observed in H69AR cells. These data implicate topoisomerase II in the **resistance** phenotype of H69AR cells, but cannot explain H69AR cell **resistance** to the Vinca alkaloids, which do not have topoisomerase II as a target. Monoclonal antibodies against antigens overexpressed on H69AR cells have been derived and four have been characterized. Immunoscreening of an H69AR cDNA expression library has allowed the identification of one of these antigens as p36 (**annexin** II), a Ca2+/phospholipid binding protein. Chemosensitizers and novel xenobiotics have been examined for their ability to circumvent the drug **resistance** of H69AR cells. The limited success of these investigations suggests that innovative approaches may be required. In conclusion, the data obtained with H69AR and other models of small cell lung cancer indicate that multiple mechanisms contribute to drug **resistance** in this disease.
CT Check Tags: Human
Antineoplastic Agents: TU, therapeutic use
***Carcinoma, Small Cell: DT, drug therapy**
Carcinoma, Small Cell: PP, physiopathology
Drug Resistance
***Lung Neoplasms: DT, drug therapy**
Lung Neoplasms: PP, physiopathology
CN 0 (Antineoplastic Agents)

L166 ANSWER 13 OF 18 CANCERLIT
AN 96042151 CANCERLIT
DN 96042151
TI Early redistribution of plasma membrane phosphatidylserine is a general feature of apoptosis regardless of the initiating stimulus: inhibition by overexpression of Bcl-2 and Abl.
AU Martin S J; Reutelingsperger C P; McGahon A J; Rader J A; van Schie R C; LaFace D M; Green D R
CS Division of Cellular Immunology, La Jolla Institute for Allergy and Immunology, California 92037, USA.
NC GM52735 (NIGMS)
SO JOURNAL OF EXPERIMENTAL MEDICINE, **(1995)**. Vol. 182, No. 5, pp. 1545-56.
Journal code: I2V. ISSN: 0022-1007.
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDL; L; Priority Journals; Cancer Journals
LA English
OS MEDLINE 96042151
EM 199601
AB A critical event during programmed cell death (PCD) appears to be the acquisition of plasma membrane (PM) changes that allows phagocytes to recognize and engulf these cells before they rupture. The majority of PCD seen in higher organisms exhibits strikingly similar morphological features, and this form of PCD has been termed apoptosis. The nature of

the PM changes that occur on apoptotic cells remains poorly defined. In this study, we have used a phosphatidylserine (PS)-binding protein (**annexin** V) as a specific probe to detect redistribution of this phospholipid, which is normally confined to the inner PM leaflet, during apoptosis. Here we show that PS externalization is an early and widespread event during apoptosis of a variety of murine and human cell types, regardless of the initiating stimulus, and precedes several other events normally associated with this mode of cell death. We also report that, under conditions in which the morphological features of apoptosis were prevented (macromolecular synthesis inhibition, overexpression of Bcl-2 or Abl), the appearance of PS on the external leaflet of the PM was similarly prevented. These data are compatible with the notion that activation of an inside-outside PS translocase is an early and widespread event during apoptosis.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Annexin V: ME, metabolism
Antigens, CD95: PH, physiology
*Apoptosis: PH, physiology
*ABC Transporters: ME, metabolism
Biological Markers
*Carrier Proteins: ME, metabolism
Cell Cycle
Leukemia, T-Cell, Acute: PA, pathology
Membrane Glycoproteins: PH, physiology
*Membrane Lipids: ME, metabolism
*Membrane Proteins: ME, metabolism
Mice
Models, Biological
Neutrophils: ME, metabolism
*P-Glycoprotein: ME, metabolism
Phagocytosis
*Phosphatidylserines: ME, metabolism
*Proto-Oncogene Proteins: PH, physiology
*Proto-Oncogene Proteins c-abl: PH, physiology
Recombinant Fusion Proteins: BI, biosynthesis
Thymus Gland: CY, cytology
Transfection
Tumor Cells, Cultured

CN 0 (phospholipid exchange proteins); **0 (Annexin V)**; 0 (Antigens, CD95); 0 (ABC Transporters); 0 (Biological Markers); 0 (Carrier Proteins); 0 (FasL protein); 0 (Membrane Glycoproteins); 0 (Membrane Lipids); 0 (Membrane Proteins); **0 (MDR2 protein)**; 0 (P-Glycoprotein); 0 (Phosphatidylserines); 0 (Proto-Oncogene Proteins c-abl); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Proto-Oncogene Proteins); 0 (Recombinant Fusion Proteins)

L166 ANSWER 14 OF 18 MEDLINE
AN 1998314838 MEDLINE
DN 98314838
TI Flow cytometric assessment of three different methods for the measurement of in vitro apoptosis.
AU Pepper C; Thomas A; Tucker H; Hoy T; Bentley P
CS Department of Haematology, Llandough Hospital, Penarth, South Glamorgan, UK.
SO LEUKEMIA RESEARCH, **(1998 May)** 22 (5) 439-44.
Journal code: K9M. ISSN: 0145-2126.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
EW 19981001
AB Chlorambucil-induced apoptosis was assessed by three different flow cytometric methods in B-cell chronic lymphocytic leukaemia (B-CLL) cells cultured in vitro and the results were compared with those derived from

the morphological assessment of the same samples. Spontaneous apoptosis was consistently observed in the control cultures in the absence of drug but this accounted for less than 12% of all cells in every case. The methods under investigation were the **Annexin** V labelling assay, the terminal deoxynucleotidyl transferase (TdT) end-labelling assay and the labelling of a 38 kDa mitochondrial membrane protein (7A6 antigen) which is exposed on cells undergoing apoptotic cell death (Apo2.7 assay). The **Annexin** V assay consistently stained a higher percentage of cells and with a greater separation between the positive and negative cell populations. We conclude that the phosphatidyl serine translocation to the outer leaflet of the cell membrane following an apoptotic signal, as labelled by **Annexin** V, probably occurs before the development of the DNA strand breaks or the exposure of 7A6 antigen in those cells triggered to die by apoptosis.

CT Check Tags: Human; Support, Non-U.S. Gov't
Annexin V: AN, analysis
*Apoptosis: GE, genetics
*Apoptosis: PH, physiology
Cell Membrane Permeability
Dyes
Evaluation Studies
*Flow Cytometry: MT, methods
Genetic Techniques
Lethal Dose 50
Leukemia, B-Cell, Chronic: PA, pathology
Propidium: AN, analysis

RN 36015-30-2 (Propidium)
CN 0 (**Annexin** V); 0 (Dyes)

L166 ANSWER 15 OF 18 MEDLINE
AN 1998447470 MEDLINE
DN 98447470
TI Apoptosis detection by **annexin** V binding: a novel method for the quantitation of cell-mediated **cytotoxicity**.
AU Shounan Y; Feng X; O'Connell P J
CS National Pancreas Transplant Unit, University of Sydney at Westmead Hospital, NSW, Australia.
SO JOURNAL OF IMMUNOLOGICAL METHODS, **(1998 Aug 1)** 217 (1-2) 61-70.
Journal code: IFE. ISSN: 0022-1759.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199901
EW 19990104
AB Current standard methods for the measurement of cell-mediated cytotoxicity rely on radioactive tracers, which either detect the release of cytoplasmic contents after plasma membrane disintegration by dying cells (51Cr release), or retained DNA by living cells (the JAM test). In this study, the **annexin** V binding assay of early apoptosis was applied to measure cell-mediated cytotoxicity. Primed human lymphocytes were examined for their ability to lyse either xenogeneic pig endothelial or allogeneic human PBMC target cells by assaying **annexin** V binding and the results compared with those obtained by the JAM test. Assaying **annexin** V binding by indirect immunofluorescence was demonstrated to be more sensitive and faster than the JAM test, which is a well-described, sensitive and simple assay for DNA fragmentation and cell death. However, the **annexin** V binding method was considered a more accurate measurement of absolute cytotoxicity as individual cell lysis was detected directly. In other methods, cytotoxic activity was calculated indirectly as a percentage of retained or released radioactive label. In addition, the apoptosis induced by the cell-mediated cytotoxicity can be visualized by this method thereby allowing a more accurate and sensitive quantitation of the number of apoptotic cells present when low effector to target ratios are used. These advantages make the **annexin** V binding method superior to other conventional

cytotoxicity assays, particularly in situations where effector cells can be easily distinguished or separated from target cells.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
***Annexin V: ME, metabolism**
*Apoptosis
***Cytotoxicity Tests, Immunologic: MT, methods**
*Cytotoxicity, Immunologic
*Leukocytes, Mononuclear: CY, cytology
Leukocytes, Mononuclear: IM, immunology
Lymphocyte Transformation
Membrane Lipids: ME, metabolism
Phagocytosis
Phosphatidylserines: ME, metabolism
Swine
CN 0 (**Annexin** V); 0 (Membrane Lipids); 0 (Phosphatidylserines)

L166 ANSWER 16 OF 18 MEDLINE
AN 97089287 MEDLINE
DN 97089287
TI Possible mechanisms of glucocorticoid--unresponsive pyrexia. Defect in lipocortin 1?.
AU Akama H; Tanaka H; Kawai S
CS Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.
SO MATERIA MEDICA POLONA, **(1995 Apr-Jun)** 27 (2) 75-8.
Journal code: LJY. ISSN: 0025-5246.
CY Poland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
EM 199702
EW 19970204
AB Glucocorticoids have a strong anti-inflammatory action, and are indispensable in the treatment of inflammatory diseases. We had a patient with the Weber-Christian disease having an intractable high fever that did not respond to even a high-dose glucocorticoid therapy, but was responsive to a nonsteroidal antiinflammatory drug. To elucidate possible mechanisms of the glucocorticoid-unresponsive fever, we have investigated the in vitro production of two eicosanoids, prostaglandin (PG)E2 and leukotriene (LT)B4, from the peripheral blood polymorphonuclear leukocytes after stimulation by ionophore A23187. The patient's leukocytes produced much larger amount of PGE2, but the same amount of LTB4, as did those of two control groups. More interestingly, the production of eicosanoids was inhibited by dexamethasone less in the patients than in the controls. Indomethacin suppressed the production of PGE2 both in the patients and in the controls. These results might be relevant in the glucocorticoid-unresponsive pyrexia.
CT Check Tags: Female; Human
Adolescence
Adult
***Annexin I: BI, biosynthesis**
Anti-Inflammatory Agents, Non-Steroidal: TU, therapeutic use
***Dexamethasone: TU, therapeutic use**
Dinoprostone: BI, biosynthesis
Dinoprostone: BL, blood
Drug Resistance
*Fever: DT, drug therapy
*Fever: ME, metabolism
Indomethacin: TU, therapeutic use
Leukotriene B4: BI, biosynthesis
Leukotriene B4: BL, blood
Middle Age
Neutrophils: DE, drug effects
Neutrophils: ME, metabolism
Panniculitis, Nodular Nonsuppurative: BL, blood
Panniculitis, Nodular Nonsuppurative: CO, complications
Panniculitis, Nodular Nonsuppurative: ME, metabolism

RN 363-24-6 (Dinoprostone); 50-02-2 (Dexamethasone); 53-86-1 (Indomethacin); 71160-24-2 (Leukotriene B4)
CN 0 (**Annexin** I); 0 (Anti-Inflammatory Agents, Non-Steroidal)

L166 ANSWER 17 OF 18 MEDLINE
AN 92372714 MEDLINE
DN 92372714
TI Detection of human anti-**annexin** autoantibodies by enzyme immunoassays.
AU Kraus M; Romisch J; Bastian B; Paques E P; Hartmann A A
CS Forschungslaboratorien der Behringwerke AG, Marburg, FRG..
SO JOURNAL OF IMMUNOASSAY, **(1992)** 13 (3) 411-39.
Journal code: HS8. ISSN: 0197-1522.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199211
AB **Annexins** belong to a family of proteins characterized by calcium-dependent binding to the cytoskeleton and phospholipid surfaces. Basing on these properties **annexins** are discussed to be involved in the regulation of cytodynamic, anticoagulatory and antiinflammatory processes. Since autoantibodies against **annexin** I had been detected in patients suffering from inflammatory or autoimmune diseases, an impact on the pathophysiological outcome was assumed. Therefore we developed solid phase, enzyme-linked immunoassays for the quantitative determination of autoantibodies directed against six members of the **annexin** family. Some preliminary results obtained from sera of patients with malignant melanoma show a quite frequent presence of such autoantibodies. These data suggest that autoantibodies are generated against all **annexins**. Furthermore, in the individual patient autoantibodies of the IgG-type are monospecific, while about 1/4 of the IgM-type are directed against several **annexins**. These observations imply that for investigation of anti-**annexin** autoantibodies in inflammatory and autoimmune diseases as well as cancer all members of the **annexin** family have to be taken into consideration.
CT Check Tags: Human
*Autoantibodies: BL, blood
*Calcium-Binding Proteins: IM, immunology
Calcium-Binding Proteins: ST, standards
*Enzyme-Linked Immunosorbent Assay: MT, methods
Enzyme-Linked Immunosorbent Assay: SN, statistics & numerical data
Enzyme-Linked Immunosorbent Assay: ST, standards
Evaluation Studies
IgG: BL, blood
IgM: BL, blood
Melanoma: IM, immunology
Reference Standards
Sensitivity and Specificity
CN 0 (Autoantibodies); 0 (Calcium-Binding Proteins); 0 (IgG); 0 (IgM)

L166 ANSWER 18 OF 18 MEDLINE
AN 92084158 MEDLINE
DN 92084158
TI Placental protein 4 as a possible tumor marker in ovarian tumors.
AU Gocze P M; Szab`o D G; Than G N; Krommer K F; Csaba I F; Bohn H
CS Department of Obstetrics and Gynecology, University Medical School, Pecs, Hungary..
SO GYNECOLOGIC AND OBSTETRIC INVESTIGATION, **(1991)** 32 (2) 107-11.
Journal code: FYA. ISSN: 0378-7346.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199203

AB Placental protein 4 (PP-4), a recently characterized glycoprotein from human placenta, was studied using a specific double-antibody radioimmunoassay in sera of 130 volunteers, 76 ovarian tumor patients and in ovarian tumor cyst fluid and ascites of 21 patients. Elevated levels (greater than 3 micrograms/l) were found in 45 of 52 ovarian cancer patients (86.5%). PP-4 levels correlated significantly with staging. 31 patients with malignant ovarian tumor were monitored on 2-9 occasions during 5-82 weeks. Rising or falling levels of PP-4 correlated with progression or regression of disease in 25 of 31 instances (80.6%). Elevated levels were found in 10 of 24 benign and borderline ovarian tumors. Elevated PP-4 level does not indicate malignancy in each case. PP-4 can be regarded as tumor-associated antigen and an tumor marker in oncological practice.

CT Check Tags: Female; Human
***Adenocarcinoma, Papillary: DI, diagnosis**
*Calcium-Binding Proteins: AN, analysis
***Cystadenocarcinoma: DI, diagnosis**
Evaluation Studies
***Ovarian Neoplasms: DI, diagnosis**
*Pregnancy Proteins: AN, analysis
Radioimmunoassay
*Tumor Markers, Biological: AN, analysis

CN 0 (**Annexin** V); 0 (Calcium-Binding Proteins); 0 (Pregnancy Proteins); 0 (Tumor Markers, Biological)

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L182 ANSWER 1 OF 6 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-031940 [04] WPIX
DNN N2001-024948 DNC C2001-009803
TI Determining the risk of developing cancer comprises determining cell sample cytotoxicity, e.g. by evaluating the affinity of the cells for at least one A1 adenosine receptor ligand.
DC B04 D16 S03
IN NEELY, C F
PA (LINK-N) LINK TECHNOLOGY INC
CYC 86
PI WO 2000070341 A2 20001123 (200104)* EN 45p G01N033-50 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 2000052693 A 20001205 (200113) G01N033-50 <--
ADT WO 2000070341 A2 WO 2000-US13102 20000512; AU 2000052693 A AU 2000-52693 20000512
FDT AU 2000052693 A Based on WO 200070341
PRAI US 1999-134276 19990514
IC ICM **G01N033-50**
AB WO 200070341 A UPAB: 20010118
NOVELTY - Determining a subject's risk for developing cancer, comprises obtaining a sample of diagnostic cells from a subject and determining a measure of cytotoxicity of the diagnostic cells for target cancer cells. The measure of cytotoxicity correlates negatively with the risk for developing cancer.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method of preventing cancer in a subject at risk of developing cancer, comprising increasing the expression of A1 adenosine receptors in the cells of the subject;

(2) a method of preventing cancer in a subject at risk of developing cancer, comprising administering a priming agent in an amount effective to prime cells;

(3) a method of preventing cancer in a subject at risk of developing cancer, comprising increasing the affinity of cells of a subject for A1 adenosine receptor ligands;

(4) a pharmaceutical liposomal formulation for the prevention of cancer in a subject determined to be at risk for developing cancer, comprising a priming agent and an activating agent encapsulated in liposomes;

(5) a diagnostic kit for determining a subject's risk for developing cancer comprising at least one reagent for determining the cytotoxicity of diagnostic cells of the subject; and

(6) a kit for preventing cancer in a subject determined to be at-risk for the development of cancer, comprising at least one reagent selected from the group consisting of reagents for increasing A1 adenosine receptor expression in cells, reagents for increasing binding of A1 adenosine receptor ligands to the cells, reagents for increasing binding of MCP-1 (undefined) protein to the cells, priming agents and activating agents.

USE - The process is used to determine a subject's risk of developing cancer and to prevent the development of cancer.

ADVANTAGE - The process can detect the likelihood of cancer before the disease even develops.

Dwg.0/5
FS CPI EPI
FA AB; DCN
MC CPI: B04-C01A; B04-E03D; B04-F02; B04-H01; B11-C08E; B12-K04A1; B14-L01; B14-L06; D05-H09; D05-H12A
EPI: S03-E14H
TECH UPTX: 20010118
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The measure of cytotoxicity is determined by evaluating the affinity of the diagnostic cells for at least one A1 adenosine receptor ligand, the number of A1 adenosine receptors on the diagnostic cells or the affinity of the diagnostic cells for MCP-1 protein. The method comprises priming the diagnostic cells by contacting the diagnostic cells with a priming agent in an amount sufficient to prime the diagnostic cells and activating the diagnostic cells by contacting the with an activating agent in an amount sufficient to induce cytotoxicity in the diagnostic cells. The priming and activating steps occur prior to determining the measure of cytotoxicity of the diagnostic cells for target cancer cells. The measure of cytotoxicity is determined by evaluating the release of cytotoxins from the diagnostic cells. The measure of cytotoxicity is determined by evaluating the percentage of target cancer cells killed by the diagnostic cells.
In the method of (1), the expression of A1 adenosine receptors in the cells of the subject is increased by transfecting the cells with a cDNA encoding the human A1 adenosine receptor, or by administering to the cells a compound selected from the group of cisplatin, daunorubicin, doxorubicin, mitoxantrone, dexamethasone and carbamazepine to increase the expression of A1 adenosine receptors in the cells of the subject.

Alternatively, the expression of A1 adenosine receptors in the cells of the subject is increased by administering to the cells an adenosine receptor antagonist (especially theophylline) in an amount effective to increase the expression of A1 adenosine receptors in the cells of the subject.
In the method (2), the priming agent is conjugated to a lipid. The method further comprises administering an activating agent in an amount effective to activate the cells. The activating agent is conjugated to a lipid. Both priming agent and activating agent are formulated together in a liposomal fraction.
In the method of (3), an allosteric enhancer for A1 adenosine receptor is administered in an amount effective to increase the affinity of the cells for A1 adenosine receptor ligands.
In the methods of (1), (2) and (3), the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.
Preferred Materials: The cytotoxin is tumor necrosis factor-alpha (TNF-alpha). The diagnostic cells are selected from the group consisting of macrophages, monocytes, promonocytes and peripheral blood stem cells. The activating agent is an A1 adenosine receptor agonist conjugated to a lipid. The priming agent is selected from phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon-gamma (IFNgamma), granulocyte-macrophage colony stimulating factor (GMCSF) and f-met-leu-phe (fMLP). The priming agent is conjugated to a lipid. The subject is human.
Preferred Kit: In the kits of (5) and (6), the reagent is a ligand for A1 receptor, ligand for MCP-1 protein, or ligand for **annexins**. The kit comprises at least one priming agent and at least one activating agent described above. The cells are macrophages, monocytes, peripheral blood stem cells and promonocytes.

L182 ANSWER 2 OF 6 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-246285 [21] WPIX
CR 1999-469130 [37]
DNN N2000-184190 DNC C2000-074515
TI Assays for determining the phagocytosis of apoptotic cells useful for identifying a compound which influences the phagocytic uptake of apoptotic cells and treats cancers and neurodegenerative diseases.
DC B04 D16 S03
IN BOGAERT, T A O E; SMITS, E; VAN CRIEKINGE, W M R
PA (DEVG-N) DEVGEN NV
CYC 87
PI WO 9964586 A2 19991216 (200021)* EN 112p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9946084 A 19991230 (200022) C12N015-12
BR 9911097 A 20010213 (200114) C12N015-12
EP 1084242 A2 20010321 (200117) EN C12N015-12
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9964586 A2 WO 1999-EP4043 19990610; AU 9946084 A AU 1999-46084 19990610; BR 9911097 A BR 1999-11097 19990610, WO 1999-EP4043 19990610; EP 1084242 A2 EP 1999-929185 19990610, WO 1999-EP4043 19990610
FDT AU 9946084 A Based on WO 9964586; BR 9911097 A Based on WO 9964586; EP 1084242 A2 Based on WO 9964586
PRAI GB 1998-20816 19980924; GB 1998-12660 19980611
IC ICM C12N015-12
ICS A61K038-17; C07K014-435; C07K014-47; C07K016-18; C12N005-10; C12N015-62; **C12Q001-68**; **G01N033-50**; **G01N033-563**
AB WO 9964586 A UPAB: 20010328
NOVELTY - Assays involving two human homologs of Caenorhabditis elegans ced-6 (h1ced-6 and h2ced-6) for identifying compounds which function as an inhibitor or an enhancer of a signal transduction pathway, is carried out

by measuring phagocytosis of apoptotic cells (AC).

DETAILED DESCRIPTION - Methods (M1-M5) for determining whether a compound (C) is an inhibitor or an enhancer of a signal transduction pathway which promotes phagocytosis of AC, comprise:

(1) exposing transfected mammalian cells (III) to apoptotic particles (AP),

(2) micro injecting/transfecting a human CED-6 protein (II) or a vector expressing RNA antisense to at least a portion of nucleotide sequence given in the specification, in a mammalian cell;

(3) exposing it to AP; and

(4) measuring the rate of uptake of AP by (III) in presence and absence of (C).

Alternately the method involves exposing (III) to the compound to be tested and antibodies against a homolog of (II), followed by quantitatively measuring the presence of any immune complexes formed between the antibodies and protein expressed by (III) which is compared to the amount of immune complex detected in (III) which has not been exposed to (C). The method may also be carried out by exposing a mammalian professional or semiprofessional phagocyte to an apoptotic mammalian cell stably transfected with a reporter gene capable of generating a signal detectable without microscopy in the presence and absence of (C) to be tested, removing any AC which are not engulfed by the phagocytes followed by detecting any signal of the reporter gene from it. Any difference in signal in the presence of (C) compared to signal in the absence of (C) is the indication that the compound is an inhibitor or enhancer of phagocytosis of AC.

INDEPENDENT CLAIMS are also included for the following:

(1) an expression vector (I), comprising a sequence of deoxynucleotides encoding a human CED-6 protein (II), comprising a fully defined amino acid sequence as given in figure 4 or 5 of the specification or its variant which differs from (II) by conservative amino acid changes;

(2) a mammalian cell line (III), transfected with (I);

(3) (C) identified by (M1), (M3), (M5);

(4) a peptide fragment (F), of a homologue (H) of (II) having amino acid sequence shown in figure 4 of the specification, having a sequence of

(a) NRAFSRKKDKTC;

(b) FLGSTEVEQPKGTE; or

(c) TRNGTQPPPVPSRST;

(5) an antibody preparation (IV), comprising antibodies directed to a epitopes of (H) such as (1), (2) or (3);

(6) a method (D1) for diagnosing a disease associated with over or under expression of (II) in phagocytic cell in an individual involves obtaining a sample of phagocytes from the individual and exposing it to (IV) to form an immune complex which is then measured quantitatively and compared with the amount of immune complex formed using phagocytes from a control individual;

(7) a fusion protein (V), which comprises (II) and a protein which is the expression product of a reporter gene;

(8) a fusion protein (VI), which comprises (II) and an epitope tag; and

(9) a method (D2) for diagnosing a disease associated with over or under expression of (II) in phagocytic cell in an individual involves obtaining a sample of phagocytes from the individual and isolating their RNA to prepare a cDNA, performing a first PCR reaction of the cDNA and then performing a second (nested) PCR on the reaction product of first PCR reaction, quantitatively and qualitatively measuring the presence of CED-6 RNA by analyzing the reaction products from the first and second PCR and then comparing the amount and type of reaction product formed in the first and second PCR with that of the reaction product formed using phagocytes from control individuals.

ACTIVITY - Cytostatic; immunosuppressive; neuroprotective; cardiant; anti-HIV. No supporting data is given.

MECHANISM OF ACTION - Apoptosis modulators.

USE - The methods are useful for identifying compounds which can act as apoptotic modulators (claimed) which are useful for treating diseases such as cancer, autoimmune diseases, neurodegenerative diseases such as

Huntington's disease, stroke, myocardial infarction and AIDS.
ADVANTAGE - The assays are well adapted for medium and high throughput screening using a multi-well plate format.
Dwg.0/34

FS CPI EPI
FA AB; DCN
MC CPI: B04-C01C; B04-E02F; B04-E08; B04-F0200E; B04-H0100E; B11-C08E1; B11-C08E5; B12-K04A; B12-K04E; B12-K04F; B14-A02B1; B14-F01; B14-F02D; B14-F08; B14-G02; **B14-H01**; B14-J01; D05-H08; D05-H09; D05-H12C; D05-H12E; D05-H14B2; D05-H17C; D05-H18
EPI: S03-E14H; S03-E14H4
TECH UPTX: 20000502

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Expression Vector: (I) comprises a reporter gene encoding green fluorescent protein-GFP positioned 5' or 3' to the sequence of deoxynucleotides shown from the transcription start codon to the transcription stop codon as given in figure 2 or 3 of the specification such that the expression of (II) or its functional variant results in expression of a reporter protein from the reporter gene. The expressed protein includes an epitope tag such as His A, at its amino or carboxy terminus.
Preferred Mammalian Cell: (III) is selected from a fibroblast or epithelial primary cell line such as COS1, BHK21, L929, CV1, SWISS 3T3, HT144, IMR32, HEPG2, MDCK, MCF7, 293, Hela, A549, SW48 or G361 (preferably COS1 cell) which are derived from human dermal FIBs, dermal keratinocytes, leukocytes, monocytes, lymphocytes, dendritic cells or macrophages.
Preferred Method: The transfected cells and the micro injected mammalian cells employed in (M1), (M2) respectively are exposed to (C) prior to addition of AP such as apoptotic neutrophils, lymphocytes, erythrocytes which have been optionally opsonized and comprise adherence cell-line PC12 or growth factor dependent mouse cell-line Ba/F3 which are rendered apoptotic by culturing in the absence of growth factor IL-3. The cells are considered apoptotic if are 20% **annexin** positive and less than 5% propidium iodide negative. The cells comprising AP are stably transfected with a reporter gene encoding beta-galactosidase, present in a plasmid with a fully defined sequence of 8578 nucleotide as given in the specification, a fluorescent protein such as GFP in which case the apoptotic cell is stably transfected with the plasmid exhibiting the expression characteristics of a plasmid shown in figure 10 or figure 29 of the specification and having a sequence as described in (9) or (28), or any protein capable of generating luminescence e.g. luciferase encoded by the reporter gene present in a plasmid exhibiting the expression characteristics of PGL2 control with the fully defined sequence of 5251 nucleotides as given in the specification. AP comprises Ba/F3 cells stably transfected with beta-galactosidase or luciferase and the level of phagocytosis is detected by adding the substrate which is converted by beta-galactosidase to a fluorescent compound. If no phagocytosis or reduced amount of phagocytosis is observed on exposure to (C) then the mammalian transfected cells are examined for viability and if viable, the phenotype of transfected mammalian cells are compared with the phenotype of untransfected mammalian cells of the same cell line. If an increased amount of phagocytosis observed in presence of (C) then the compound is exposed to an untransfected mammalian cell of the same cell line and observed whether the compound induces the same phenotype exhibited by the transfected mammalian cell. Antisense RNA employed in (M3) comprises a sequence of nucleotides which are capable of hybridizing to a nucleotides sequence shown in figure 2 or 3 of the specification under the conditions of stringency which are higher than 2XSSC; 0.1%SDS; 25-50degreesC. The phagocyte employed in (M5) is a mouse macrophage cell line J774 or a human monocyte cell line THP-1 obtained by culturing a monocyte cell-line under suitable conditions to differentiate it into macrophages prior, to exposure to AP. The phagocyte could also be a transgenic cell transfected with (I) which comprises a fully defined sequence of 6121 nucleotides as given in the specification, encoding the cell surface receptor CD36. The phagocytes are cultured in multiwell plates and the apoptotic cell and test compound are added to the individuals wells. The signal from the reporter gene employed in any of the above methods is detected by a

automatic plate reader capable of detecting a fluorescent signal and the phagocytic uptake to be measured in any of the above methods, is carried out is by non-microscopic means such as multiwell plate reader which measures luminescence, fluorescence or performs spectrophotometric detection. (M5) preferably employs the above mentioned detection methods. PCR in (D2) is carried out with primers derived from (II) or from the vector used in the generation of cDNA.
Preferred Antibody: (IV) comprises polyclonal antibodies.
Preferred Fusion Protein: (V) is obtained by expressing GFP and h1ced-6 encoding sequence which has the fully defined sequence of 5619 or 5628 nucleotides as given in the specification. (VI) is obtained by expressing HisA and h1ced-6 encoding sequences which has the fully defined sequence of 5021 nucleotides as given in the specification.

L182 ANSWER 3 OF 6 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-013265 [01] WPIX
DNC C2000-002536
TI New method for screening for agents which alter a cellular phenotype, used for identifying agents for treating e.g. tumors, allergy, asthma or psychiatric disorders.
DC B04 D16
IN FISHER, J; LORENS, J; PAYAN, D; ROSSI, A
PA (RIGE-N) RIGEL PHARM INC
CYC 84
PI WO 9954494 A2 19991028 (200001)* EN 88p C12Q001-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9935654 A 19991108 (200014)
EP 1071809 A2 20010131 (200108) EN C12Q001-00 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9954494 A2 WO 1999-US8345 19990416; AU 9935654 A AU 1999-35654 19990416; EP 1071809 A2 EP 1999-917563 19990416, WO 1999-US8345 19990416
FDT AU 9935654 A Based on WO 9954494; EP 1071809 A2 Based on WO 9954494
PRAI US 1998-157748 19980921; US 1998-62330 19980417
IC ICM **C12Q001-00**
AB WO 9954494 A UPAB: 20000105
NOVELTY - A novel method of screening for a bioactive agent capable of altering a cellular phenotype comprises:
(a) combining at least one candidate bioactive agent and a population of cells; and
(b) sorting the cells in a fluorescence activated cell sorting (FACS) machine by separating the cells on the basis of at least 5 cellular parameters.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of screening for a bioactive agent capable of altering a cellular phenotype, comprising:
(a) introducing a library of nucleic acids each encoding a candidate bioactive agent into a population of cells; and
(b) sorting the cells in a FACS machine by separating the cells on the basis of at least 3 cellular parameters.
USE - The methods can be used for identifying agents for treating disorders involving exocytosis, e.g. allergy, asthma, rhinitis, psychiatric disorders or Chediak-Higashi syndrome and similar disorders in mice, mink, cattle, cats, and killer whales. They can also be used for identifying agents for treating disorders involving cell cycle regulation such as cancers. They can also be used for identifying agents which alter other cellular phenotypes, e.g. small molecule toxicity or the expression of moieties e.g. receptors (particularly cell surface receptors), adhesion molecules, cytokine secretion, or protein-protein interactions.
ADVANTAGE - The method can provide for the screening of large numbers of bioactive agents in a relative short period of time.
Dwg.0/11

FS CPI
FA AB; DCN
MC CPI: B04-F01; B11-C07B3; B12-K04E; D05-H09
TECH UPTX: 20000105
TECHNOLOGY FOCUS - BIOTECHNOLOGY - In preferred methods, the cellular phenotype is exocytosis and the cellular parameters are selected from light scattering, fluorescent dye uptake, fluorescent dye release, **annexin** granule binding, surface granule enzyme activity, and the quantity of granule specific proteins, or the cellular phenotype is cell cycle regulation and the cellular parameters comprise cell viability, proliferation and cell phase.

L182 ANSWER 4 OF 6 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-337419 [28] WPIX
DNN N1999-252873 DNC C1999-099183
TI Modulating or assessing **multidrug** resistance related to **annexin** proteins.
DC B04 D16 S03
IN GEORGES, E; WANG, Y
PA (UYMC-N) UNIV MCGILL; (GEOR-I) GEORGES E; (WANG-I) WANG Y
CYC 83
PI WO 9921980 A1 19990506 (199928)* EN 62p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9896174 A 19990517 (199939) C12N015-12
CA 2219299 A1 19990424 (199940) EN C12N015-12
EP 1025225 A1 20000809 (200039) EN C12N015-12
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9921980 A1 WO 1998-CA992 19981026; AU 9896174 A AU 1998-96174 19981026; CA 2219299 A1 CA 1997-2219299 19971024; EP 1025225 A1 EP 1998-949842 19981026, WO 1998-CA992 19981026
FDT AU 9896174 A Based on WO 9921980; EP 1025225 A1 Based on WO 9921980
PRAI CA 1997-2219299 19971024
IC ICM C12N015-12
ICS A61K031-70; A61K038-02; A61K038-17; A61K039-395; A61K048-00; C07K014-47; C12N015-11; **C12Q001-18**; **C12Q001-68**; **G01N033-50**; **G01N033-53**; **G01N033-574**
AB WO 9921980 A UPAB: 19990719
NOVELTY - Isolated nucleic acid (I) encoding an **annexin** family member (II), i.e. a member of the **MDR** (**multidrug** resistance) gene family, for assessing or modulating **MDR** in a cell, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method for detecting and assessing **annexin**-based **MDR** by treating test sample with an oligonucleotide (ON) containing 10-50 nucleotides (nt) that hybridize specifically to RNA and/or DNA encoding an **annexin**, ON being complementary to a sequence of at least 10 consecutive nt from the sequences for **annexins** I to IX, and detecting any hybrids formed;
(2) kits for this method;
(3) recombinant vector for modulating, inhibiting and/or increasing **annexin**-based **MDR** in a cell, containing (I) linked to a promoter;
(4) cells containing this vector;
(5) a method for identifying compounds that affect **annexin** -based **MDR** by incubating with test compound in presence or absence of a drug and assessing any effect of the test compound on resistance to the drug;
(6) a method of reducing **annexin**-based **MDR** by administering a nucleic acid, (dominant negative) mutant of **annexin**, antibody to **annexin**, peptide or small molecule;

(7) pharmaceutical composition for reducing **MDR** comprising **annexin**-based **MDR**-affecting compound and a carrier; and
(8) methods for diagnosing presence of, or predisposition to, **annexin**-based **MDR** in a patient or pathogen.
ACTIVITY - Antitumor; antifungal.
MECHANISM OF ACTION - None given.
USE - Antisense sequences from (I), or any other agent that inhibits (II), are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of (II), or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. (II) can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing (II) expression in plants may be used to develop specific resistance.
Dwg.0/9
FS CPI EPI
FA AB; DCN
MC CPI: B04-A0800E; B04-B03C; B04-E02F; B04-E05; B04-E08; B04-F01; B04-F05; B04-G01; B04-H01; B04-N02; B04-N03; B04-N04; B04-P0100E; B11-C08E5; B12-K04A1; B12-K04F; D05-H09; D05-H11; D05-H12A; D05-H12D1; D05-H12D2; D05-H12E; D05-H14; D05-H16A
EPI: S03-E14H
TECH UPTX: 19990719
TECHNOLOGY FOCUS - BIOLOGY - Preferred Process: Assessment/modulation of **MDR** can be done in an animal, mammalian, human, parasitic or fungal cell. Suitable compounds for testing as modulators are nucleic acid, (dominant negative) mutants of **annexins**, antibodies, peptides or small molecules, specifically antisense nucleic acid, calcium chelators or calcium channel blockers. To diagnose presence of, or predisposition to, **annexin**-based **MDR**, a sample (from patient or pathogen) is analyzed to determine the amount of **annexin** protein and/or RNA present. Any increase in the level, relative to a control, indicates **MDR**.
Preferred Nucleic Acid: (I) is at least 90% identical with a sequence encoding any of **annexins** I to IX, or their complements. Specifically it encodes **annexin** I (P40) for which the 346 amino acid sequence is given in the specification (together with the 1399 nt encoding sequence).
Preferred Vector: The recombinant vector is pCDNA3/P-40 or pC1N4P-40.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: Overexpression of a protein, designated P40, has already been noted in several **MDR** cell lines. Monoclonal antibody IPM96, specific for P40, was used to screen a cDNA library from HeLa cells and two positive clones isolated. The inserts from these clones were sequenced; both encoded the 346 amino acid protein noted above. Analysis of databases showed that this sequence is identical with **annexin** I. **Annexin** I is not phosphorylated in **MDR** cells. Analysis of **MDR** cells with monoclonal antibodies specific for other **annexins** showed that **annexins** II and IV were also overexpressed (but to a lesser degree than was **annexin** I). The full-length sequence for P40 has been cloned into the expression vectors pcDNA3 and pCIN4 for subsequent transfection of cells.

L182 ANSWER 5 OF 6 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-153790 [13] WPIX
DNC C1999-045517
TI New isolated human **annexin** binding protein - used to develop products for treating e.g. neurological disorders, cancers, immune disorders, infections or trauma.
DC B04 D16
IN CORLEY, N C; HILLMAN, J L; SHAH, P
PA (INCY-N) INCYTE PHARM INC
CYC 82
PI WO 9906560 A1 19990211 (199913)* EN 62p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9885964 A 19990222 (199927) C12N015-12
US 5932712 A 19990803 (199937) C07H021-04

ADT WO 9906560 A1 WO 1998-US15599 19980728; AU 9885964 A AU 1998-85964 19980728; US 5932712 A US 1997-903801 19970731

FDT AU 9885964 A Based on WO 9906560

PRAI US 1997-903801 19970731

IC ICM C07H021-04; C12N015-12
ICS A61K038-17; C07K014-47; C07K016-18; C12N001-21; C12N005-10; C12N015-63; C12N015-85; C12Q001-68

AB WO 9906560 A UPAB: 19990331
The following are claimed: (1) a purified **annexin** binding protein (NABP-1) comprising an amino acid sequence (I) of 290 amino acids in length, or fragments; (2) a purified variant of NABP-1 having at least 90% amino acid identity to sequence (I) and which retains at least one functional characteristic of the NABP-1; (3) an isolated and purified polynucleotide sequence (PNS) encoding an NABP-1 as in (1) or fragments or variants of the PNS; (4) a PNS which hybridises to a PNS as in (3); (5) a PNS which is complementary to a PNS as in (3) or fragments or variants; (6) an isolated and purified PNS comprising sequence (II) of 1434 nucleotides in length or fragments or variants; (7) a PNS which is complementary to a PNS as in (6); (8) an expression vector containing at least a fragment of a PNS as in (3); (9) a host cell containing a vector as in (8); (10) a purified antibody which specifically binds to a polypeptide as in (1); (11) a purified agonist of a polypeptide as in (1), and (12) a purified antagonist of a polypeptide as in (1).

USE - NABP-1 is expressed in cancerous tissue, tissues associated with inflammation and immune responses, and neural tissues. NABP-1 appears to play a role in cancer, immune disorders, and neurological disorders. In particular, decreased expression or activity of NABP-1 appears to be associated with neurological disorders, while increased expression or activity of NABP-1 appears to be associated with cancer and immune disorders. NABP-1 polypeptides and agonists can be used to treat neurological disorders e.g. akathesia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, cerebral neoplasms, dementia, depression, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, **multiple** sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, schizophrenia or Tourette's disorder. Antagonists of NABP-1 can be used to prevent or treat cancers or immune disorders e.g. AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anaemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythema nodosum, atrophic gastritis, glomerulonephritis, gout, Graves' disease, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, **multiple** sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis, complications of cancer, haemodialysis, extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections and trauma. The products can also be used for detection, diagnosis and **drug** screening.

Dwg.0/3

FS CPI

FA AB

MC CPI: B04-E02F; B04-E03F; B04-E05; B04-E08; B04-F0100E; B04-G01; B04-N02; B04-N0200E; B11-C08E5; B12-K04; B14-G03; B14-H01; B14-J01; B14-J07; B14-S01; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H13; D05-H14; D05-H17A6

L182 ANSWER 6 OF 6 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1999-045948 [04] WPIX

DNN N1999-033450 DNC C1999-014607

TI Cell apoptotic activity determination - comprises contacting cell population with medium containing apoptotic specific diagnostic reagent and diagnostic accessory reagent and determining activity of diagnostic accessory reagent.
DC B04 D16 S03
IN ARMSTRONG, R C; DIAZ, J; FRITZ, L C; TOMASELLI, K J
PA (IDUN-N) IDUN PHARM INC
CYC 22
PI WO 9855863 A1 19981210 (199904)* EN 57p G01N033-50 <--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9878177 A 19981221 (199919) G01N033-50 <--
EP 988545 A1 20000329 (200020) EN G01N033-50 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9855863 A1 WO 1998-US11571 19980605; AU 9878177 A AU 1998-78177 19980605; EP 988545 A1 EP 1998-926308 19980605, WO 1998-US11571 19980605
FDT AU 9878177 A Based on WO 9855863; EP 988545 A1 Based on WO 9855863
PRAI US 1997-869553 19970605
IC ICM **G01N033-50**
AB WO 9855863 A UPAB: 19990127
A single-well, microscale method of determining the specific activity of a cell comprises contacting a cell population of 1 multiply 105 cells for 30-240 minutes with a volume of a medium containing an apoptotic specific diagnostic reagent (I) and a diagnostic accessory reagent (II) to cover the cell population, and determining the activity of (II).

The cell population comprises > 10000-50000 (especially 100000) cells. The time of the contact is especially 60 minutes. The volume of the medium is 1-200 (especially 30-125) mu l. (I) comprises also a caspase specific substrate attached to a detectable label or **Annexin** V, or is selected from ZEVD-AMC, YVAD-AMC and DEVD-AMC. (II) is a lysis reagent or calcium. The cells are cells which overexpress a cell survival polypeptide which is sufficient to prevent the induction of apoptosis by a direct stimulus selected from Fas ligand, anti-fas antibody, staurosporine, UV and gamma -irradiation. The cell survival polypeptide is selected from Bcl-2, Bcl-xl, Mcl-1 and E1B-19K, which are encoded by a homologous or heterologous exogenic nucleic acid. The compounds tested for the apoptosis inducing activity also comprises a compound which induces caspase activity or inhibits the activity of a cell survival protein in a cell.

The method can also be carried out in a multi-well format for simultaneous determination of different samples. The cells are exposed to a direct stimulus of the cell death pathway. The method also comprises lysing the cells and determining the caspase activity in the lysate. Alternatively, the cells are contacted with **Annexin** 5 and determining the amount of bound **Annexin** 5.

USE - The method is used to test compounds for their effect on cell apoptosis, which can be useful in the treatment of cancer. The method can also identify compounds which inhibit cell apoptosis.

ADVANTAGE - The method rapid.

Dwg.0/3
FS CPI EPI
FA AB
MC CPI: B04-F01; B11-C08; B12-K04; **B14-H01**; D05-H09
EPI: S03-E14H

=> d his

(FILE 'HOME' ENTERED AT 08:06:01 ON 11 APR 2001)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:06:32 ON 11 APR 2001
E WO98-CA992/AP,RPN
L1 1 S E3
E GEORGES E/AU

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L2          57 S E3,E5,E6
               E WANG Y/AU
L3        3678 S E3-E40
               E WANG YING/AU
L4        1675 S WANG YING?/AU
L5        5407 S L2-L4
L6           3 S L5 AND ANNEXIN
               E ANNEXIN/CW
L7        1662 S E3,E4
               E ANNEXIN/CT
L8        1662 S E3-E23
               E E13+ALL
L9        2164 S E21,E20+NT
L10          2 S L5 AND L7-L9
L11          3 S L6,L10,L1
L12          3 S L5 AND (P40 OR P 40)
L13          1 S L12 AND L11
L14          5 S L11-L13
               E MULTIDRUG/CT
               E E4+ALL
L15       2332 S E4+NT
L16       2340 S E5
               E E8+ALL
L17       1062 S E4+NT
L18       1531 S E11+NT
               E E11+ALL
L19       1873 S GLYCOPHOSPHOPROTEINS/CT (L) P
L20        837 S GLYCOPROTEINS/CT (L) P
               E DRUG RESISTANCE/CT
               E E3+ALL
L21      26554 S E3+NT
               E E13+ALL
L22       4016 S E2
L23         41 S L5 AND L15-L22
L24          2 S L23 AND L7-L9
L25         25 S L23 AND L18-L20
L26         12 S L15,L16 AND L25
L27         17 S L21,L22 AND L25
L28         17 S L26,L27
L29          2 S L14,L24 AND L28
L30          5 S L14,L24,L29
L31          4 S L30 NOT THROMBOSIS/TI
L32         15 S L28 NOT L31
L33         19 S L31,L32
L34         23 S L23-L32 NOT L33
L35         11 S L34 AND MULTIDRUG (L) RESIST?
L36          6 S L34 AND MDR?
L37         16 S L31,L35,L36
L38         16 S L31,L37
L39         11 S L34 NOT L38
L40          2 S L39 AND (IMMUNOASSAY OR DOXORUBICIN)/TI
L41         18 S L38,L40
               SEL RN

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L43         12 S L42 AND SQL/FA
L44          3 S L43 AND (346 OR 1338 OR 1399)/SQL
L45        266 S ANNEXIN
L46        267 S L44,L45

    FILE 'HCAPLUS' ENTERED AT 08:32:26 ON 11 APR 2001
L47        138 S L46
L48          2 S L47 AND L5
L49         18 S L41,L48
L50       3013 S L7,L8,L9 OR ANNEXIN OR L47
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L51        2070 S L50 AND (PD<=19981026 OR PRD<=19981026 OR AD<=19981026 OR PY<
L52          11 S L51 AND L15-L17,L21,L22
L53           4 S L51 AND MDR?
L54          10 S L51 AND MULTIDRUG (L) RESIST?
L55          12 S L52-L54
L56        2211 S L15-L17,L21,L22 AND L18-L20
L57        2381 S MULTIDRUG (L) RESIST? AND L18-L20
L58        1923 S MDR? AND L18-L20
L59           4 S L56-L58 AND (P40 OR P 40)
L60          16 S L55,L59
L61          12 S L60 NOT L41
                E P-GLYCOPROTEIN/CT
                E E4+ALL
L62        1531 S E11+NT
L63           9 S L5 AND L62
L64           8 S L63 AND L15-L17,L21,L22
L65           8 S L63 AND MULTIDRUG (L) RESIST?
L66           5 S L63 AND MDR?
L67          24 S L41,L64-L66
L68           0 S L63 NOT L67
L69         929 S L62 AND L15-L17,L21,L22
L70        1090 S L62 AND (MULTIDRUG (L) RESIST? OR MDR?)
L71        1162 S L69,L70
L72           4 S L71 AND L51
L73          36 S L60,L61,L67,L72
                E DRUG SCREENING/CT
                E E3+ALL
L74       12105 S E2,E1+NT
                E E7+ALL
L75        3151 S E3
                E E13+ALL
L76        1577 S E5+NT
L77       11320 S E9+NT
L78       63573 S E10+NT
                E TEST KIT/CT
                E E4+ALL
L79        2840 S E2+NT
L80          49 S L51 AND L74-L79
L81         167 S L18-L20,L62 AND L74-L79
L82           2 S L80 AND L81
L83          70 S L15-L17,L21,L22 AND L80,L81
L84          72 S MULTIDRUG(L)RESIS? AND L80,L81
L85          62 S MDR? AND L80,L81
L86          51 S L83-L85 AND (PD<=19981026 OR PRD<=19981026 OR AD<=19981026 OR
L87          84 S L73,L82,L86
L88           6 S L87 AND 9/SC,SX
L89          12 S L87 AND ANNEXIN?
L90           1 S L87 AND P40
L91           5 S L87 AND P 40
L92          18 S L88-L91

     FILE 'HCAPLUS' ENTERED AT 08:53:04 ON 11 APR 2001
L93        3014 S L7,L8,L9 OR ANNEXIN?
L94          65 S L93 AND L74-L79
L95          62 S L94 NOT L92
L96          46 S L80 NOT L92
L97          62 S L95,L96
L98           9 S L47 AND L74-L79 NOT L92
L99          64 S L97,L98
L100          0 S L99 AND MULTIDRUG?
L101          0 S L99 AND MDR?
L102          8 S L99 AND 9/SC
L103          6 S L99 AND 9/SX
L104         14 S L102,L103
L105         12 S L104 AND ANNEXIN?/CW
L106          2 S L104 NOT L105
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L107          1 S L106 NOT ANNEXING/AB
L108         13 S L105,L107

     FILE 'BIOSIS' ENTERED AT 08:58:16 ON 11 APR 2001
L109         14 S L46
L110       2761 S ANNEXIN
L111       2762 S L109,L110
L112       1719 S L111 AND PY<=1998
                E GEORGES E/AU
L113          0 S E3-E5 AND L111
L114          1 S L112 AND MDR?
L115          6 S L112 AND (MULTIDRUG OR MULTI DRUG)
L116          5 S L115 AND RESIST?
L117          5 S L114,L116
L118          2 S CHEMORESIS? AND L112
L119          6 S L117,L118
L120        177 S L112 AND 240?/CC
L121          6 S L120 AND L119

     FILE 'BIOSIS' ENTERED AT 09:05:44 ON 11 APR 2001

     FILE 'CANCERLIT' ENTERED AT 09:05:55 ON 11 APR 2001
L122          0 S L46
L123        796 S ANNEXIN
                E ANNEXIN/CT
                E E79+ALL
L124        423 S E6+NT
L125        796 S L123,L124
L126        464 S L125 AND PY<=1998
L127          2 S L126 AND MDR?
L128          5 S L126 AND MULTIDRUG (L) RESIST?
                E DRUG RESISTANCE, MULTIPLE/CT
                E E3+ALL
L129      15808 S E3+NT
                E E4+ALL
                E E3+ALL
L130         14 S L126 AND L129
L131         15 S L127,L128,L130
L132         10 S L131 AND C4./CT
L133         10 S L131 AND NEOPLASMS+NT/CT
L134          8 S L131 AND TUMOR CELLS, CULTURED+NT/CT
L135         13 S L132-L134
L136          2 S L131 NOT L135

     FILE 'MEDLINE' ENTERED AT 09:12:12 ON 11 APR 2001
L137       1615 S ANNEXINS+NT/CT
L138       2911 S ANNEXIN OR L137
L139       1942 S L138 AND PY<=1998
L140          2 S L139 AND P40
L141          0 S L139 AND P 40
                E GLYCOPROTEIN/CT
L142        339 S E55+NT/CT AND L139
                E E55+ALL
L143        117 S E39+NT AND L139
L144         21 S E39,E41,E42 AND L139
                E DRUG RESISTANCE/CT
L145         18 S E3+NT/CT AND L139
                E E3+ALL
L146          2 S L145 AND L140-L144
L147         18 S L145,L146
                E SCREENING/CT
                E E4+ALL
                E E2+ALL
L148          9 S E11+NT AND L139
L149          2 S E37+NT AND L139
L150         10 S L148,L149
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L151          1 S L147 AND L150
L152         27 S L147-L151
L153         18 S L152 AND RESIST?
L154          1 S L152 AND MDR?
L155         18 S L153,L154
L156         12 S L152-L155 AND C4./CT
L157         12 S L152-L155 AND NEOPLASMS+NT/CT
L158          7 S L152-L155 AND TUMOR CELLS, CULTURED+NT/CT
L159         15 S L156-L158
L160          5 S L152-L155 AND D22./CT
L161          8 S L152-L155 AND ANTINEOPLASTIC AGENTS+NT/CT
L162         16 S L159-L161
L163         11 S L152-L155 NOT L162
L164          1 S L163 AND CYTOTOX?/TI
L165         17 S L162,L164

     FILE 'CANCERLIT, MEDLINE' ENTERED AT 09:22:59 ON 11 APR 2001
L166         18 DUP REM L135 L165 (12 DUPLICATES REMOVED)

     FILE 'CANCERLIT, MEDLINE' ENTERED AT 09:23:12 ON 11 APR 2001

     FILE 'WPIX' ENTERED AT 09:23:30 ON 11 APR 2001
               E ANNEXIN
L167        135 S E2-E7
L168          1 S L167 AND MULTIDRUG
L169          1 S L167 AND (MULTI OR MULTIPLE)(L)DRUG
L170          2 S L167 AND MDR?
L171          3 S L168-L170
L172         22 S (B14-H01 OR C14-H01 OR B12-G07 OR C12-G07)/MC AND L167
L173         26 S P633/M0,M1,M2,M3,M4,M5,M6 AND L167
L174         30 S L172,L173
L175         10 S L174 AND G01N/IC
L176          9 S L174 AND C12Q/IC
L177         11 S L174 AND N102/M0,M1,M2,M3,M4,M5,M6
L178         15 S L175-L177
L179         15 S L174 NOT L178
L180          5 S L178 AND (C12Q001-00 OR G01N033-50)/IC
L181          7 S L171,L180
L182          6 S L181 NOT C07F/IC

     FILE 'WPIX' ENTERED AT 09:38:01 ON 11 APR 2001
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